

INTENSITY-MODULATED RADIOTHERAPY OF HEAD AND
NECK CANCER AIMING
TO REDUCE DYSPHAGIA: EARLY DOSE-EFFECT
RELATIONSHIPS OF THE
SWALLOWING STRUCTURES

Dr. P. Vijay Karan Reddy, MDRT, Cancer Institute (WIA), Adyar,
Chennai

AIM:

To elicit clinical advantages of sparing of swallowing structures, the pharyngeal constrictors (PC), glottic and supra-glottic larynx (GSL) and the esophagus. The primary end point of this study was to analyze dysphagia in patients treated with modified IMRT strategy and the secondary end point was to compare incidence and severity of dysphagia in a retrospective study where the same structures were not spared.

MATERIAL AND METHODS:

This is a prospective longitudinal study. The period of study was May 2013 to May 2014. A total of 26 patients, aged 16 to 70yrs being treated with concurrent chemo-radiation with cisplatin for nasopharyngeal and oropharyngeal carcinoma (Stage I-IV) with histology of SCC and NPC were considered for this study. The IMRT strategy used was optimized to spare the PC, GSL, and esophagus with a constraint to reduce the volume of these structures receiving more than 50Gy. The dose-effect relationship of these structures compared to clinical presentation was assessed. The clinical assessment of patients was done both subjectively with the help of the HNQOL instrument and objectively using penetration and aspiration score (PAS) in modified barium swallow.

The clinical benefit of such a IMRT strategy was analyzed and compared to a retrospective group of patients in who the same swallowing structures were not given any dose constraints.

RESULTS:

Significant correlations were observed between barium swallow based dysphagia and the mean doses to the PC, GSL and Esophagus, as well as the partial volumes of these structures receiving 50–60 Gy; the highest correlations were associated with doses to the superior PC ($p = 0.001$). Significantly worse dysphagia was found post treatment (Pre vs Post – 34% vs 27%) 73% of the patients had no dysphagia and 3 (7.6%) of the patients were gastric tube dependent (1with

aspiration). Compared to standard IMRT strategy – incidence of dysphagia significantly decreased (7.6% compared to 18%).

CONCLUSION:

These dose–volume-effect relationships provide initial IMRT optimization goals and motivate further efforts to reduce swallowing structures doses to reduce dysphagia and aspiration. When compared patients in whom the structures were not spared, there was a significant improvement in dysphagia.

INTRODUCTION

In the recent past, therapy for head-and-neck cancer has changed dramatically resulting in more intense treatment regimens. The intensification of treatment has resulted in improved loco-regional control rates and survival, but resulted in severe acute and late toxicities among which dysphagia stands out.

Swallowing is a programmed motor behavior, which occurs within seconds and around 600 to 1000 times a day and takes not more than 20 seconds each time (1). It requires stimulation of sensory nerves in the oropharynx. In this phenomenon there is a requirement of precise co-ordination of more than thirty muscles and six cranial nerves, with actions, which are both involuntary and voluntary (2). Swallowing has two important features: passage of the food from the oral cavity to the stomach and the protection of the airway, which if impaired may lead to aspiration. It becomes an important factor depicting the quality of life of patients with head and neck cancers. Functional or structural defects of the oral cavity, pharynx, larynx and esophagus may lead to dysphagia. Dysphagia rehabilitation includes identifying and treating abnormalities of feeding and swallowing and also maintaining safe and efficient digestion and hydration. For the evaluation and treatment of defects and disorders of eating and swallowing, understanding the pathophysiology

and physiology is essential.

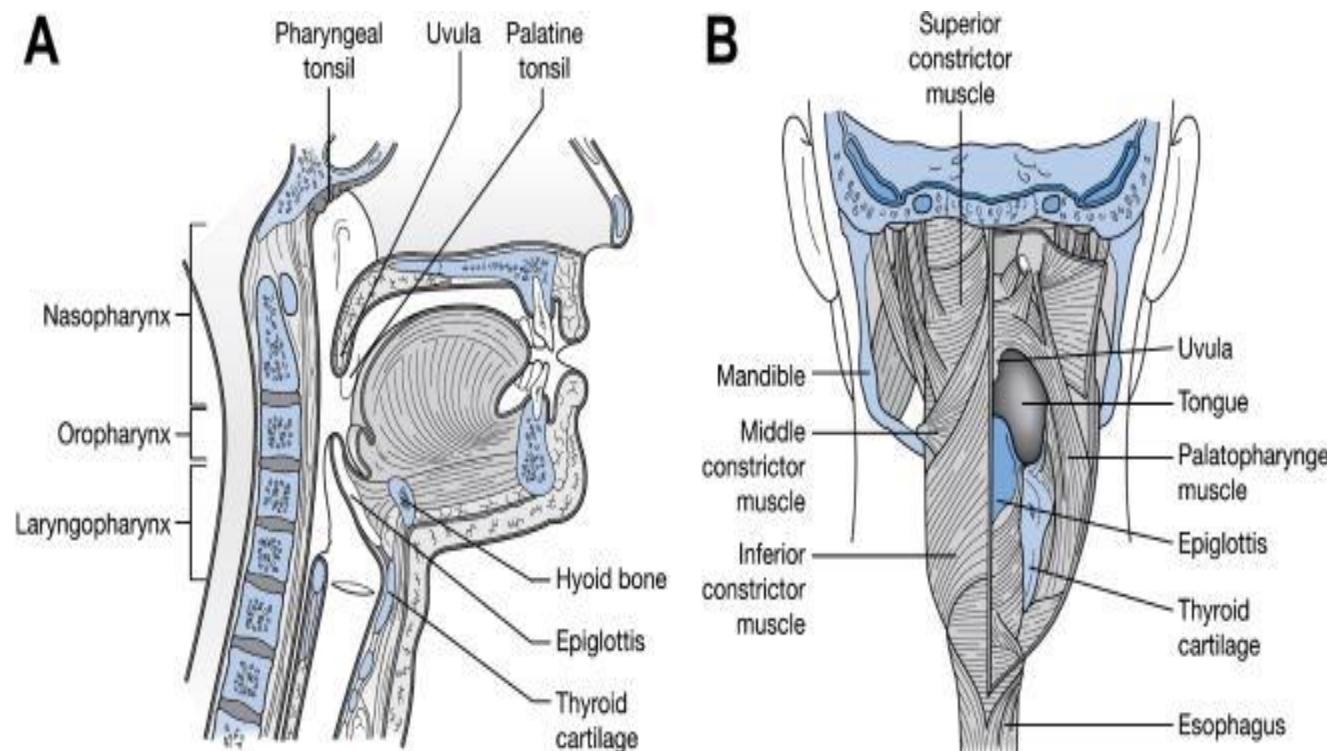
1.1 ANATOMY:

Structures involved in swallowing are:

- Oral tongue
- Faucial pillars
- Base of tongue
- Epiglottis
- Pharyngeal Constrictors
- Supraglottic and glottic larynx
- Esophagus

The tongue has consists of two surfaces i.e., both oral and pharyngeal surfaces. The faucial pillars separate the oral cavity from pharynx. The constrictor muscles of the pharynx originate from the thyroid cartilage anteriorly and the hyoid bone and cranium posteriorly and insert into the posterior median raphe. Similarly the origin of the sub mental muscles is from the mandible and they are attached to the tongue and hyoid bone. It is attached to the hyoid bone anteriorly. Anteriorly the sides of the cricoid cartilage attaches to the cricopharyngeus muscle. The cricopharyngeus muscle facilitates the closure of the upper esophageal sphincter by compressing in into the back of the cricoid cartilage. The

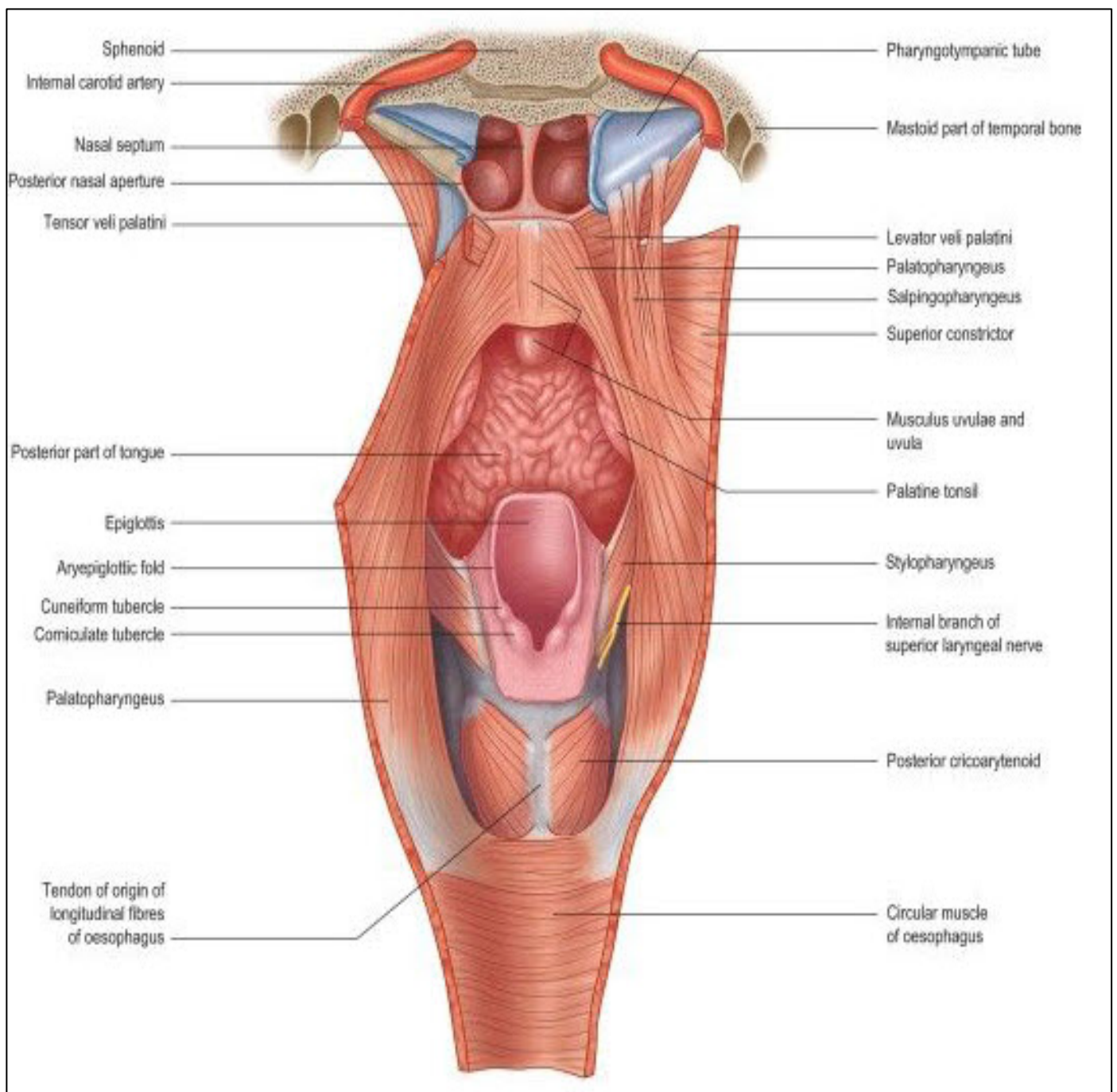
larynx gives rise to the epiglottis, which is angled upward and backward and inserts into the hyoid bone anteriorly. The vallecula is a space between the epiglottis and pharyngeal surface of the tongue. The laryngeal surface of epiglottis along with the true and false vocal cords together forms the larynx. The upper end of the larynx continues into the lower portion of the pharynx. Pyriform recesses are spaces in the pharynx which are present on either side of the larynx, lateral to it.



Innervation of major muscles related to swallowing

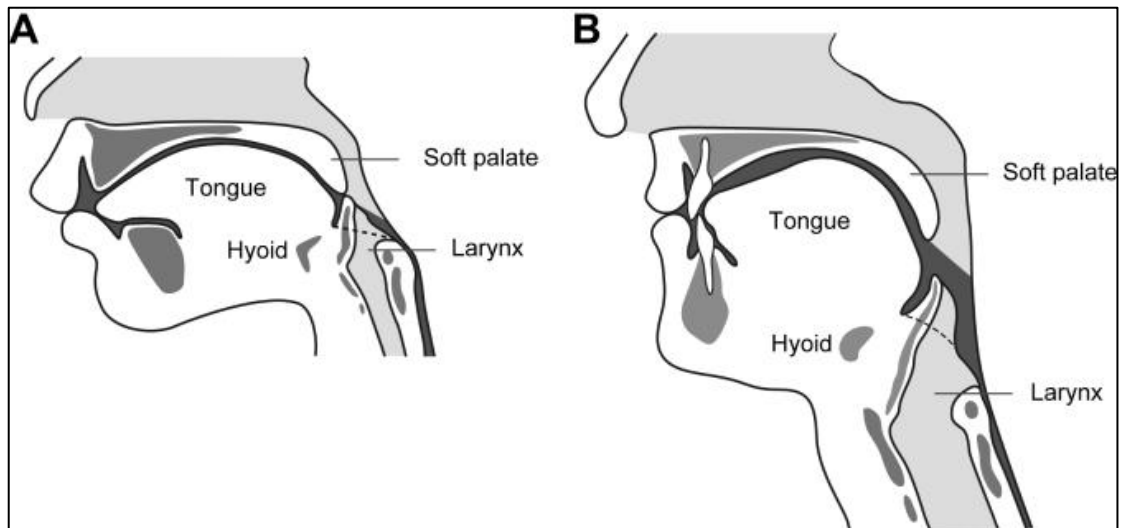
Cranial Nerves	Muscles
Trigeminal Nerve (V)	<p>Tensor Veli Palitini</p> <p>Mylohyoid</p> <p>Masticatory muscles</p> <p>Anterior belly of digastrics</p>
Facial Nerve (VII)	<p>Facial muscle</p> <p>Stylohyoid</p> <p>Posterior belly of digastrics</p>
Glossopharyngeal Nerve (IX)	Stylopharyngeous
Vagus Nerve (X)	<p>Levator levi palitini</p> <p>Palatopharyngeous</p> <p>Salpingopharyngeous</p> <p>Intrinsic laryngeal muscles</p> <p>Cricopharyngeus</p> <p>Pharyngeal constrictors</p>
Hypoglossal Nerve (XII)	<p>Intrinsic tongue muscles</p> <p>Hyoglossus</p> <p>Genioglossus</p>

	<p>Styloglossus</p> <p>Geniohyoid</p> <p>Thyrohyoid</p>
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1.1 Development of Anatomy:

There is a difference in anatomy of the head and neck in both infants and adults. In the infant, there is no eruption of teeth, there is a flatter hard palate and the larynx and hyoid are placed up higher in the neck to the oral cavity. The epiglottis contacts the soft palate posteriorly so that the larynx is open to the Nasopharynx. A soft tissue barrier separates the airway from the oral cavity. However, with development there are some anatomical changes seen in the pharynx in adult humans. The larynx descends to a lower position in the neck during growth. There is no contact of the soft palate with the epiglottis, thus making the pharynx longer vertically. The development of speech is thus contributed by this change in human development. We become vulnerable for aspiration as pharynx becomes a part of both the food way and the airway.



A) The tongue and palate are flatter and the oral cavity is small in the human infant.

The epiglottis is nearly attached to the soft palate. Only during swallowing the air way and food way are separated B) the larynx is lower in the neck, and the food way and airway cross over in the pharynx in an adult.

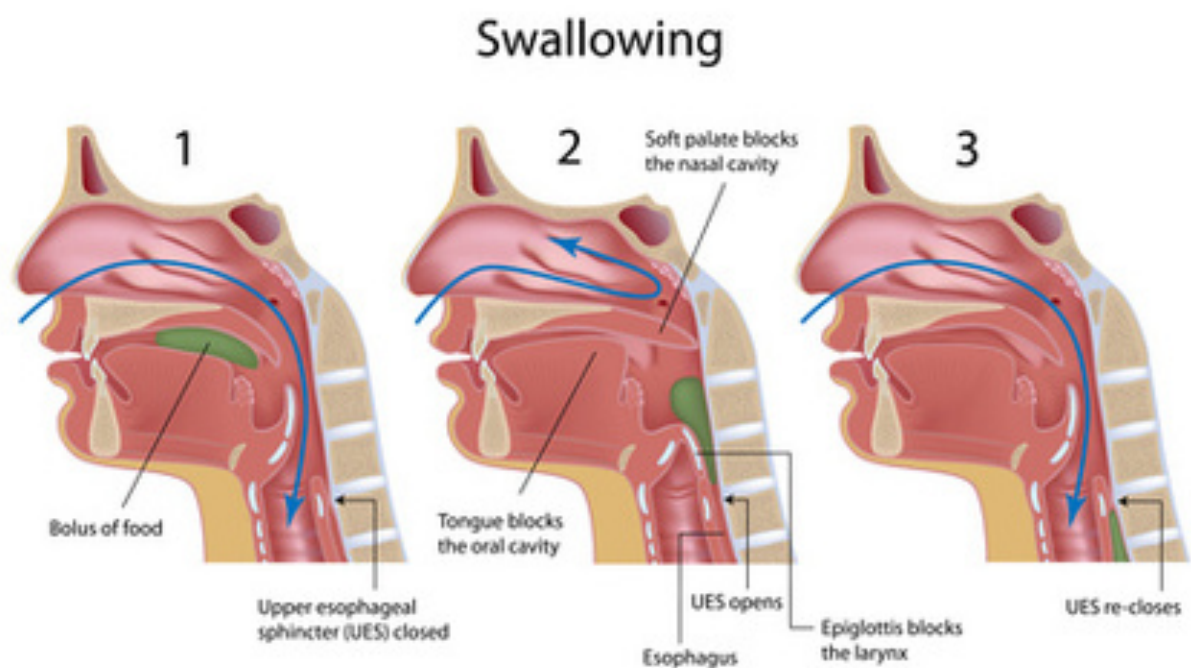
1.2 PHYSIOLOGY:

Swallowing is described as the transportation of a food bolus or liquid bolus from the oral cavity to the stomach through the pharynx and esophagus. A smooth coordinated process, which involves a complex series of both voluntary and involuntary neuromuscular contractions, constitutes 'normal deglutition'. This complex involuntary and voluntary neuromuscular process involves higher brain centers like tract of nucleus solitarius, nucleus ambiguous along with the cranial nerves V, VII, IX, X, and XII. There are two models, which were earlier described to study the normal physiology of eating and swallowing:

- *Four Stage Model* for drinking and swallowing liquids
- *Process Model* for eating solid food.

However a three-stage sequential model was used to describe normal swallow in human beings. Based on location of the bolus the swallowing process was classified into three phases (3,4):

- Oral phase
- Pharyngeal phase
- Esophageal phase



Subsequently the Four Stage Model was introduced by subdividing the oral phase into oral preparatory and oral propulsive phases. This Four Stage Model was used to adequately describe the process and movement of a liquid bolus through the swallowing process but could not account for the movement and swallowing of a solid bolus. Therefore, the Process Model of Feeding was introduced to describe the swallowing of a solid bolus (5,6).

ORAL PHASE:

Contraction of muscles of tongue and striated muscles of mastication



Bolus is first positioned in the middle of tongue, on the dorsal surface



Bolus is pressed firmly against the tonsillar pillars



Sensory neurons are triggered



Begins the pharyngeal phase

The first phase of swallowing is controlled by the motor nuclei of the trigeminal, facial and hyoglossal cranial nerves. This is also the involuntary part of this phase. The oral phase is further subdivided into:

- Oral preparatory phase
- Oral propulsive phase

Oral preparatory phase: This phase basically involves making the bolus swallow able.

Liquid bolus taken into the mouth through cup/straw



Bolus held in the anterior part of floor of mouth or on the tongue surface
against hard palate



Simultaneously the oral cavity is sealed by the contact of the soft palate
and tongue posteriorly – prevents leakage into the oro-pharynx

Oral propulsive phase

The tip of tongue elevates to touch the alveolar ridge of hard palate



Simultaneously the posterior tongue drops to allow the bolus into oropharynx

The liquid bolus is squeezed into the pharynx when the tongue surface moves upwards expanding the area of tongue and palate contact from anterior to posterior. In case of a liquid bolus the pharyngeal phase begins during the oral propulsive phase.

Oral Stage for Solid Food (Process Model of Feeding) :

The process of normal eating in humans, especially food transport and bolus formation in the oropharynx could not be described adequately by the Four Stage Sequential Model (3-6). The bolus is formed in the oropharynx when chewed and moistened food passes through the tonsillar fauces in a healthy subject eating solid food. The pharyngeal stage of swallowing happens several seconds after this stage of swallowing. While the chewing continues in the oral cavity, the food can pass into the oropharynx and accumulate there. The events described in the Process Model were first observed in mammalian studies (8) and later applied in

humans (5). The same does not stand good for the Four Stage Model, as there is an overlap of the oral preparatory, propulsive and pharyngeal phases.

1) *Stage I transport* - When food is ingested into the mouth, the tongue carries out three steps:

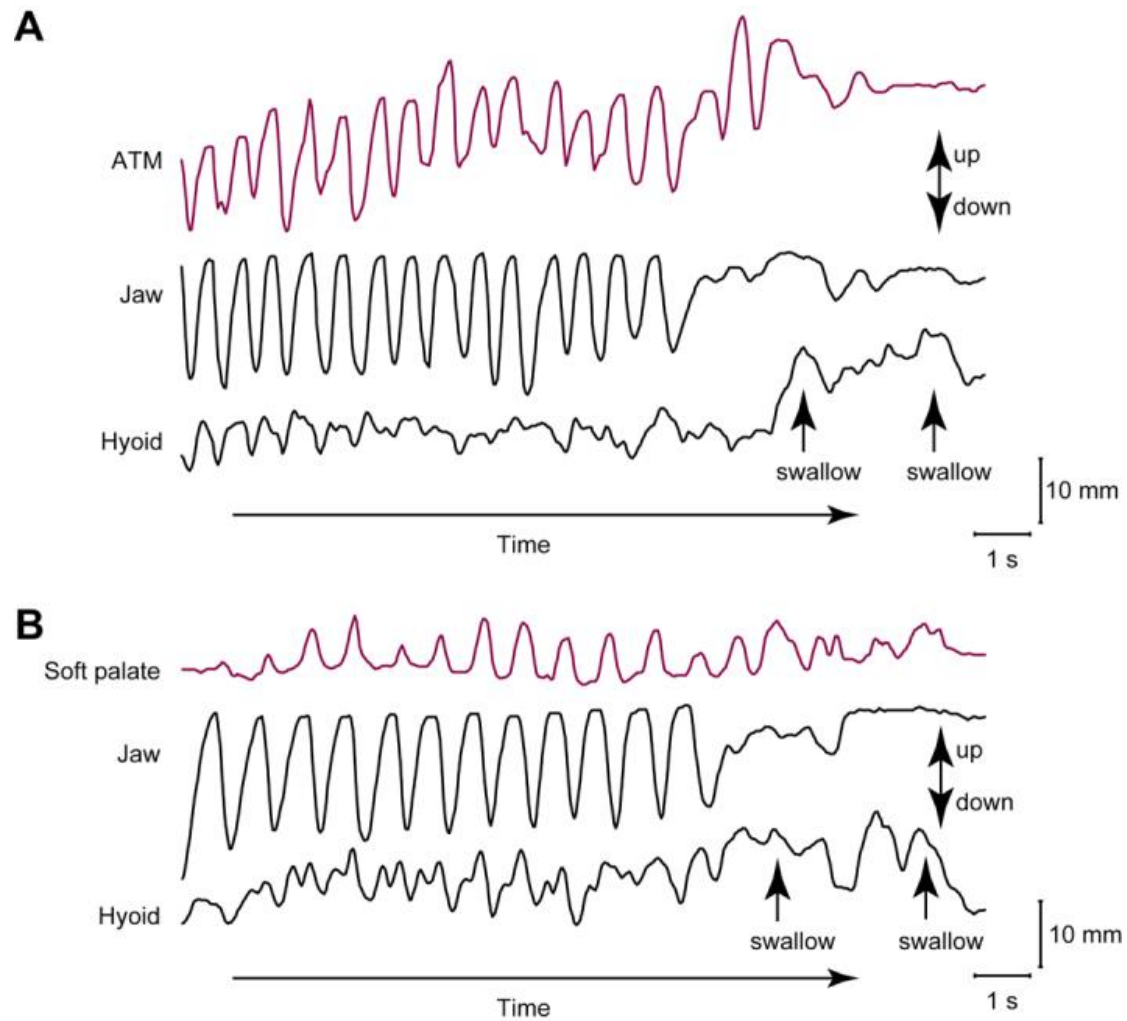
- The food is taken to the post-canine region
- Rotates laterally,
- Places the food onto the occlusal surface of lower teeth for food processing.

2) *Food processing* – Stage transport is immediately followed by food processing. This stage involves making the consistency of bolus ideal for swallowing. This is accomplished by reducing the size of the ingested food and making it soft with the help of salivation and this entire process continues until all the food is ready for swallowing. A smooth but tight co-ordination between the cyclic movement of the jaw and the movements of the tongue, cheek, soft palate and hyoid bone is essential for swallowing.

During drinking of liquid, the bolus is held in the oral cavity by the sealing of the posterior oral cavity by tongue-palate contact during the oral preparatory stage. Whereas during the food processing stage, there is

open communication between the oral cavity and the pharynx which is facilitated by the cyclical movement of the tongue and soft palate along with the jaw movement (6,9). Thus, the posterior oral cavity is not sealed during eating. The food's aroma is delivered to the chemoreceptors in the nose by the movements of the jaw and tongue which pumps air into the nasal cavity through the pharynx (10-12).

The jaw movement is coordinated with the cyclical movement of tongue during processing. These movements are particularly large in the antero-posterior and vertical dimensions for the tongue (13) and the same in the vertical dimension for the jaw. The tongue moves forward and downward during jaw opening and reaches its anterior most point during mid or late jaw opening. This cyclical tongue movement with the jaw can cause us to bite our tongue and for the same reason the tongue moves backwards as well during late jaw opening. During chewing, the tongue moves medio-laterally and also rotates on its antero-posterior axis (14). The food is kept on the occlusal surfaces of teeth by the coordination of the tongue movements with the cheek movements. The hyoid bone is connected with the cranial base, mandible, sternum and thyroid cartilage through the suprahyoid and infrahyoid muscles and due to which it plays an important role in the movement of the tongue and jaw.



Movements of the jaw, hyoid and tongue A) or soft palate B) over time. Vertical positions of A) the anterior tongue marker (ATM), lower jaw and hyoid bone and B) soft palate, lower jaw and hyoid bone, each in a complete feeding sequence. Movement towards the top of the figure is upwards. Positions of the structures are plotted relative to the upper jaw over time. Rhythmic movement of the tongue and soft palate is temporarily linked to cyclic jaw movement. The hyoid also moves rhythmically; the amplitude of hyoid motion is greater in swallowing than in processing cycles.

2) *Stage II Transport:* When the ingested food becomes suitable for swallowing it is propelled through the fauces into the oropharynx after being placed on the surface of the tongue. This phase of swallowing is similar to that of the oral propulsive phase of swallowing for a liquid bolus. As it is in the propulsive phase for a liquid bolus, the tongue first comes in contact with the hard palate just behind the upper incisors and subsequently from forward to backward the area of tongue-palate contact increases which in turn squeezes the bolus back against the palate and finally into the oropharynx. This phase of swallowing is primarily driven by the tongue and does not require gravity (15,16). Food processing cycles can be interposed with the phase of bolus transport. Once the food is transported into the oropharynx, it accumulates in the pharyngeal surface of tongue and valleculae. If there is food remaining in the oral cavity, chewing continues and the bolus in oropharynx increases in size by the subsequent transport cycles. In normal individuals the duration of transport phase which includes bolus aggregation after food processing range from a fraction of a second to about ten seconds (6).

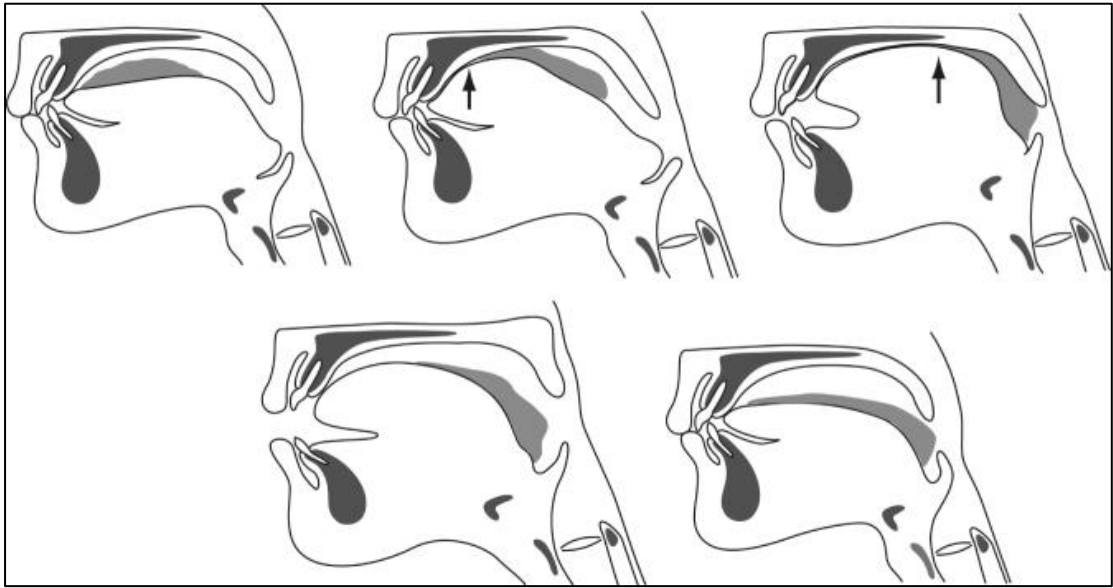


Figure depicting phase-II Transport

PHARYNGEAL PHASE:

The pharyngeal phase is the shortest but the most complex phase as it does not involve any pharyngeal activity until the swallowing reflex is triggered. It is completely involuntary when compared to other phases of swallowing. The swallowing reflex lasts for only 1 second and involves the motor and sensory tracts from glossopharyngeal and vagus cranial nerves. Pharyngeal phase of swallowing is an important, rapid, involuntary phase of swallowing which lasts only for about a second and includes two crucial features:

- *Food passage* – involves the basic passage of food from the pharynx through the UES into the esophagus.
- *Airway protection* – To prevent the food from entering the airway by moving the larynx and trachea away from the pharynx.

When a food particle accidentally enters the larynx, reflex, which immediately tries to expel the same, is known as “*cough reflex*”.

In this phase of swallowing, the bolus is made to enter into the pharynx without allowing regurgitation of food bolus in to the Nasopharynx and this is accomplished when the soft palate elevates and closes the Nasopharynx.

The base of tongue retracts



Bolus pushed against PPW



Constrictor muscles contract, squeezing the bolus downward



Pharynx also reduces in volume by shortening vertically

The critical aspect of this phase of swallowing is to prevent the food bolus from entering the larynx and this is possible with the help of various protective mechanisms. The mechanisms involved in preventing aspiration include

- Prior to opening of UES, the arytenoids bend forward to contact epiglottis and vocal cords close the larynx (17,18).
- The thyrohyoid and supra-hyoid muscles contract to pull the hyoid bone and larynx upward and forward allowing the larynx to be tucked behind base of tongue.
- Finally, the backward tilt of the epiglottis closes the laryngeal vestibule.

It is unclear how this tilting of epiglottis occurs, but may probably be due to (19):

- Elevation of Hypopharynx and larynx
- Constriction of pharynx
- Movement of bolus
- Retraction of tongue base

The entry of bolus into the esophagus is facilitated by the opening of the UES, which consists of constrictor muscles mainly inferior group, cricopharyngeus muscle and proximal part of esophagus. Tonic muscle

contraction (20,21) allows the closure of the UES. Three important factors contribute to the UES opening.

- Cricopharyngeus muscle relaxation: this relaxation either occurs prior to the UES opening or the arrival of the bolus.
- The opening of the UES is also achieved by pulling the hyolaryngeal framework forward. This is facilitated by the contraction of the supra-hyoid muscles and thyrohyoid muscles.
- The UES distends due to pressure of the approaching bolus which in turn assists in its opening (22).

The active process of UES opening by the contraction of the supra hyoid and thyro-hyoid muscles is the most important mechanism of all. This sphincter opening differs from other such openings in the body, as it is an active process unlike others, which are passive.

The pharyngeal phase of swallowing occurs as follows:

Pharyngeal peristalsis- Contraction of the superior constrictor and BOT
propelling the bolus backward



Cessation of respiration (expiration)



The bolus is driven around the opening of the pharynx by the elevation of
the larynx and retro-flexion of the epiglottis



The base of epiglottis and arytenoids are approximated



Dilatation of UES further propels the bolus into the esophagus



The bolus is then allowed to enter the upper esophagus by the relaxation
of the constrictors and the UES.

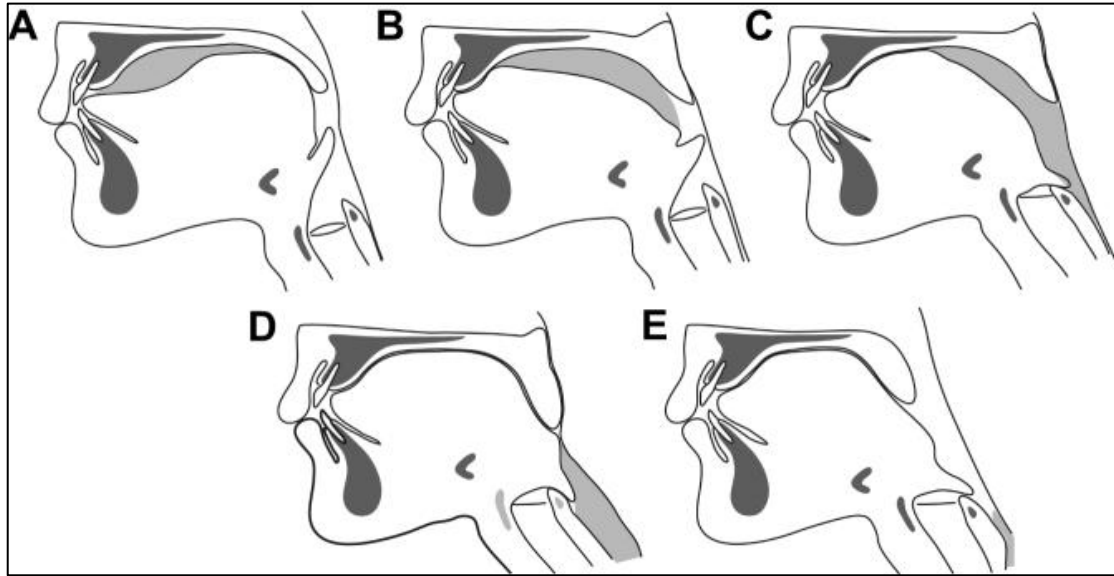


Diagram of liquid bolus swallowing

ESOPHAGEAL PHASE:

Anatomically, esophagus is a tubular structure that extends from the UES to the LES. The LES is kept closed at rest by the tonic smooth muscle contraction to prevent the regurgitation from stomach. The esophagus can broadly be divided into upper one third and lower two thirds. The upper one third is innervated by skeletal muscles and lower two thirds by smooth muscle. The transport of bolus is different in the thoracic esophagus when compared to the pharynx because it is controlled by the autonomic nervous system and is true peristalsis. The food bolus from the pharynx reaches the upper esophagus through the UES and at this point a peristaltic wave begins in the esophagus, which

carries the bolus to the stomach through the LES. The esophageal peristalsis wave consists of two main components:

- First the bolus is accommodated in the esophagus by a wave of relaxation.
- The bolus is then propelled down by a wave of contraction.
- In an upright position, gravity helps.

Bolus location at swallow initiation in normal swallows:

Swallowing is elicited as a measure of position of the head of the bolus relative to the time of pharyngeal swallow. The commonly used marker for this measurement is the point where the x ray shadow of the ramus of mandible crosses the pharyngeal surface of the tongue. Earlier it was assumed that the pharyngeal swallow is triggered when the head of food bolus passes the fauces as per VF. Delayed swallow initiation is when the bolus crosses the lower border of the mandible more than 1 second before swallow initiation. It is considered as an important finding as the larynx is open at this point when the bolus is approaching.

However, it was recently found that in healthy individuals drinking liquids the pre-swallow bolus enters into the pharynx also (23-25). The chewing bolus is furthermore accumulated in the oropharynx or valleculae prior to swallowing. It is now known that the position of the

bolus at swallow initiation is quite variable and is especially true when the bolus has both solid and liquid components. Saitoh et al. said that the leading edge of the food often entered the hypo-pharynx before swallowing in healthy young adults when the food bolus has both solid and liquid components. And because of this the liquid reaches the larynx when it is open.

At swallow initiation and in case of swallowing of liquid it alters the location of the bolus. When the larynx remains closed between swallows, before pharyngeal swallow initiation the bolus head often reaches the valleculae (23,26-29).

Peristaltic contractions propel the bolus for about 27cm from the cricopharyngeus through the thoracic esophagus

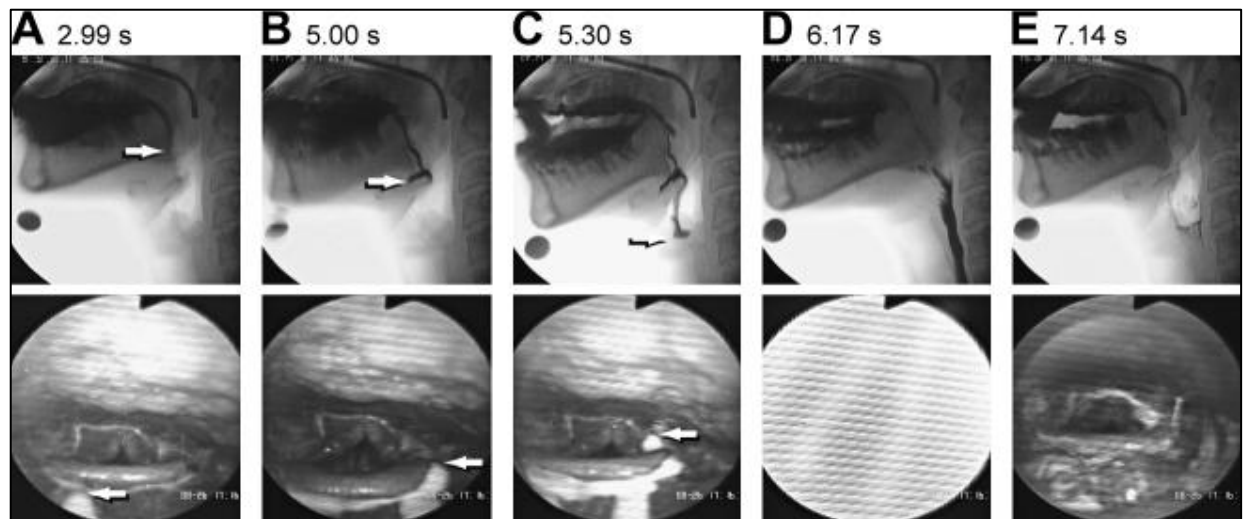


The bolus reaches the gastric cardia when the LES relaxes

Coordination among eating, swallowing and breathing:

Breathing along with eating and swallowing are tightly and precisely coordinated. In normal individuals, swallowing is dominant over breathing (30-32). During swallowing breathing ceases briefly not only because of the physical attribute of the tilting of epiglottis and arching of soft palate but also because of the neural suppression of breathing at the brain stem (31). Swallowing usually starts with the expiratory phase of breathing when drinking a liquid. When swallowing, respiration ceases for about 0.5s to 1.5s and continues to be in the state and breathing resumes in the expiration phase (33-35). This is considered to be a protective mechanism to prevent the left over food in the larynx entering into the larynx (36). Where as during sequential swallowing, while drinking from a cup respiration restarts with inspiration (37).

As with liquids, when eating solid food also the respiratory rhythm is altered. The rhythm is altered right from the onset of mastication. During mastication, the respiratory cycles duration decreases but with swallowing, the “exhale – swallow – exhale” temporal relationship holds good (32,38,39). However, the breaks are longer, sometimes beginning much before swallow onset (12,39,40).



VFG and FEES images of bolus entry in the pharynx with two-phase

1.3 DYSPHAGIA:

Dysphagia is derived from the Greek words '*dys*', meaning difficulty and '*phagia*' meaning to eat (1). Dysphagia occurs due to a mechanical obstruction or neurological disassociation leading to disruption of peristalsis, which impairs the transport of a liquid or a solid food bolus along the pharyngo-esophageal conduit. The common complaint of patients with impaired swallowing is that they find it difficult to initiate swallowing or feeling of food sticking or stopping on its way to the stomach. The cause of dysphagia could either be functional or organic (41,42). Dysphagia could be either episodic or start with difficulty for solids and gradually worsen. Episodic dysphagia, which occurs for both liquids and solids usually, suggests a motor disorder. When the dysphagia is initially for solids and gradually worsens to liquid

diet, it usually suggests a functional deficit or a structure and in case of a similar progression, which is more rapid and associated with weight loss, it is thought to be malignant. From a clinical point of view it is essential to identify whether it is oropharyngeal or esophageal dysphagia.

Dysphagia may also lead to severe complications like:

- Dehydration
- Malnutrition
- Pneumonia
- Airway obstruction

Dysphagia could be due to either structural or functional abnormalities.

Structural Abnormalities:

The structural abnormalities causing dysphagia can be either congenital or acquired. One commonly seen congenital abnormality is the cleft lip and palate. Due to this abnormality the labial control for sucking is impaired, the oral suction is decreased, difficult to maintain the oral pressure and causes nasal regurgitation, as there is insufficient velopharyngeal closure. The mastication also is impaired due to the under growth of the palate and mal alignment of the teeth.

Some of the other congenital structural abnormalities are:

- Cervical osteophytes – commonly seen in the elderly. As the name suggests, they are outgrowths from the cervical vertebrae. They tend to direct the food into the airway as the food pathway is narrowed ($\sim 50\%$) (43).
- Diverticula – is a pouch, which may be present in the pharynx or the esophagus. It usually occurs in a weak spot in the muscular walls. A Zenker diverticulum occurs in the Hypopharynx with its opening at the cricopharyngeus but the body may be much lower (44). From the diverticulum the bolus can be regurgitated into the pharynx causing cough or aspiration.
- Webs or strictures – They obstruct the food passage and usually more symptomatic with solid food than liquids. They may occur anywhere from the sphincters to pharynx or esophagus. The common site for such strictures is narrowing at the UES.

Failure to open the UES may be due to weakness of muscles or due to webs or strictures i.e. it might be structural or functional (45). In such cases dilatation is the intervention of choice but at the same time it gets difficult to differentiate such conditions. The most common site for a stricture to occur is the body of the food pipe i.e. esophagus. It is often

diagnosed in patients with GERD (gastro-esophageal reflux disease) but esophageal carcinoma should always be considered in the differential diagnosis as it is a serious condition and appropriate and timely intervention can improve both the survival and quality of life.

Functional Abnormalities:

Oral Cavity:

Functional Abnormalities affecting any of the parts of oral cavity i.e., the cheek, jaw, lips or tongue can impair the food-processing phase.

- Drooling caused by reduced closing pressure of lips.
- Leakage of the bolus into the pharynx, mainly liquids due to weak and premature contraction of the tongue and soft palate.
- Trapped food in between lower teeth and cheek or gums i.e. buccal or labial sulci due to weakness of buccal or labial muscles.
- Incoordination and weakness of tongue can cause impaired mastication and bolus formation and transport. In some cases sensory deficit also produces similar impairments and also excessive retention of food in oral cavity after swallowing.
- In the same way Xerostomia also impairs food processing, bolus formation and transport (46).

- Masticatory performance is reduced by any loss of teeth. Due to this reduced performance chewing could be delayed and particle size of swallowing bolus might be larger.
- In patients with carcinomas of the head and neck being treated with chemo radiation therapy are often found to be symptomatic due to delay in swallowing initiation, reduced pharyngeal transport, and insufficient laryngeal protection (47).

Pharynx:

In pharynx, any impairment of its function can cause defects in initiation of swallowing, propulsion of the bolus, and formation of bolus and retention of food in the pharynx after completion of swallowing.

- Reduction in pressure during pharyngeal swallow affecting the transport through UES and regurgitation of food to the Nasopharynx may occur due to insufficient velo-laryngeal closure.
- Insufficient force of pharyngeal propulsion causing retention of all or a part of the food bolus in the pharynx, usually in the valleculae and pyriform sinuses may be due to impaired tongue base retraction or weakness of pharyngeal constrictors.

- In case of high viscosity boluses, there may be obstruction of bolus propulsion and retention of food in the valleculae due to incomplete tilting of the epiglottis.
- Increased risk of aspiration of the food retained in the piriform sinuses and Hypopharynx after swallow may occur due to impaired opening of the UES causing obstruction of the food way either partially or totally. Impaired opening of the UES can be caused either by fibrosis or inflammation resulting in increased stiffness of the sphincter or failure to relax the sphincter musculature. Also, weakness of another set of muscles, which normally pull the sphincter open during swallowing, can cause impaired UES opening and these muscles are the anterior suprahyoid muscles.

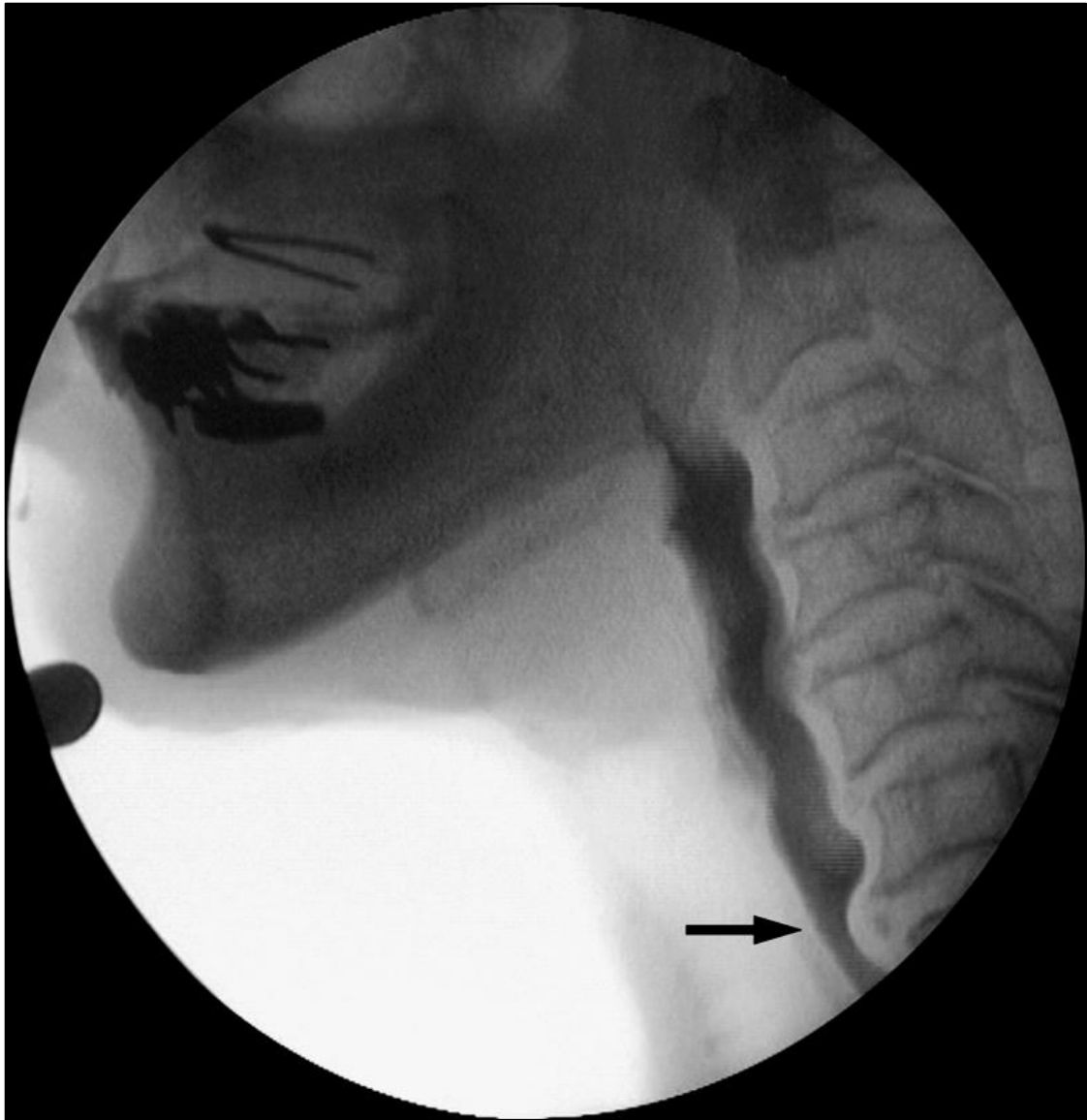
Esophagus:

Next is, esophageal dysfunction. This is common compared to oral cavity or pharynx and characteristically does not often show any symptoms.

Motor disorders of the esophagus include conditions, which are of:

- Hyper-activity (e.g. spasm)
- Hypo-activity (e.g. weakness) or
- Incoordination of the musculature (48)

Any of the above conditions can lead to retention of food in the esophagus due to inadequate or ineffective peristalsis. This food retention in esophagus after swallowing may cause regurgitation of the food into the pharynx, which may lead to aspiration of the regurgitated material. Sometimes these motor disorders are caused by gastro esophageal reflux disease, and can sometimes respond to treatment with proton pump inhibitors (PPIs).



Cervical Osteophytes – 50% luminal narrowing noted in a barium swallow in a patient with C6-C7 (arrow) osteophyte.

Protection of airway – penetration/aspiration

Airway protection is an integral and the most essential feature of the whole process of swallowing. Failure at any level to protect the airway may lead to serious consequences.

Laryngeal penetration is observed when the processed food bolus from the oral cavity or the regurgitated material from the esophagus or retained food particles in the pharynx enters the larynx just above the level of true vocal cords.

Aspiration is defined when the same food bolus entering the larynx passes through the vocal folds.

We can observe laryngeal penetration in some normal individuals as well but in case of aspiration, which is noted in endoscopy or fluoroscopy is considered to be pathological, and in such a case there is always a high risk of obstruction of airway and aspiration pneumonia (49). Such an aspiration can occur anytime either before, during or after swallowing. For clinical purposes the mechanism of aspiration should be noted if observed in fluoroscopy or endoscopy. Mechanism of airway protection during the swallow can be impaired by:

- Reduced elevation of hypo-laryngeal framework

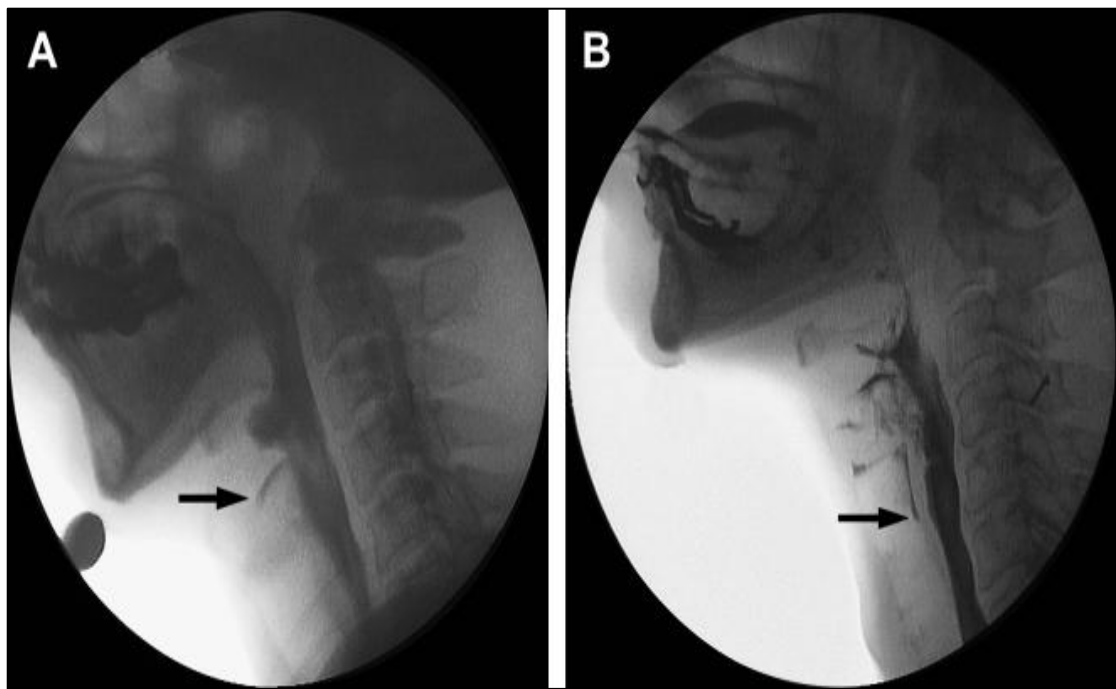
- Impairment of epiglottic tilt
- Incomplete closure of the laryngeal vestibule
- Inadequate vocal cord closure due to weakness or paralysis, or fixation.

Aspiration before the swallow is commonly caused by:

- Liquids entering into the pharynx directly (due to impaired hold in the oral cavity)
- Laryngeal closure occurring after a bolus is already entered into the larynx

And lastly, aspiration occurring after the swallow is usually due to residual food bolus in the pharynx after the swallow. The material could be inhaled when breathing is resumed after completion of the swallow.

The subsequent consequences due to aspiration can be very variable, ranging from no apparent effect all the way to complete airway obstruction or even severe pneumonia. In normal healthy individuals, the response to aspiration is strong cough or throat clearing but in individuals suffering from severe dysphagia the laryngeal sensation is often abnormal (50). Aspiration in which there is no apparent clinical response or Silent aspiration has been reported in 25-30% of individuals who have been referred for dysphagia evaluations (50,51,52).



Penetration and Aspiration

VF images of laryngeal penetration and aspiration in dysphagic patients swallowing liquid barium. Arrow indicates the leading edge of barium.

The effect of aspiration in an individual can be determined by many factors including:

- Quantity of the aspirate
- Depth of the aspiration material in the airway
- Physical properties of the aspirate (if the material is acidic it is most damaging to the lung, causing chemical pneumonitis)
- Individual's pulmonary clearance mechanism.

Risk of bacterial pneumonia is increased by an aspirate in an individual who maintains poor oral hygiene (53).

Oropharyngeal Dysphagia:

Complaint - Difficulty getting the food bolus to the back of the throat or that food gets stuck in the back of the throat.

Signs –Include cough reflex, regurgitation through the nose and the individual choking immediately after swallowing. They also face a greater difficulty swallowing the liquids than solids.

Esophageal Dysphagia:

Complaint – Food sticking in the sub sternal region or the sternal notch.

Signs – To determine the timing of the symptom by observing the patient swallow. In case of esophageal dysphagia, the onset of dysphagia sensation occurs several seconds after swallowing begins.

Evaluation of Dysphagia:

Physical examination:

- To rule out pre-existing disorders general history regarding body habits, history of drooling and current mental status should be noted.
- The PPW motion on phonation and movement of the palate (elevation) should be inspected in the oropharynx.
- The presence of pooled secretions in the larynx makes it difficult to examine the larynx, which is very essential for evaluation of dysphagia.

Investigations:

- *Plain films* – Inflammatory (epiglottitis, retro-pharyngeal abscess)
- *Barium esophagram* – Can be used in individuals in whom structural defects are suspected.
- *Manometer* – Barometric measurement of the intra-luminal pressures. Rarely used.

- *Bolus Scintigraphy* – Used to follow the progress of a patient, with history of aspiration or to follow esophageal emptying.
- *Video-fluoroscopy or modified barium swallow* – “GOLD STANDARD”, to assess the proper functioning of the oral and the pharyngeal phases of the process of swallowing.
- *Endoscopy* – Direct pharyngoscopy or upper GI endoscopy or esophagography is the initial diagnostic study of choice in a patient who has a history of esophageal dysphagia, and the history suggesting the presence of a pharyngeal or esophageal lesion.

1.4 Dysphagia in Head and Neck Cancers:

Dysphagia as a presenting symptom and also treatment related dysphagia is an important factor influencing the treatment tolerance and QOL of patients with head and neck cancers. Previously, surgery followed by adjuvant therapy was the standard of care for such patients. With the advent of the concept of organ and function preservation aiming at a better quality of life for such patients, there also has been intensification of therapy regimens in order to improve tumour control rates. The same has been achieved but with the consequence of added morbidity and an effect on post treatment QOL. The aim of radiation for malignancy of any site is to achieve maximum dose conformity to the tumour site and least possible dose exposure to the surrounding normal

tissue. This depicts the intensity and rate of incidence of associated side effects of treatment. The main sequela related to these intensified regimens for patients with head and neck malignancy is dysphagia (54).

Several studies have proven improved overall survival and better tumour control rates when RT alone in head and neck cancers was compared to RT concurrent with cisplatin and one such landmark study was the Radiation Therapy Oncology Group (RTOG) 91-11. In this study however, when toxicity profile in terms of dysphagia was observed, it was found that at the end of one year post therapy 23% of the patients were not able to eat solid or liquid food in the chemo-RT arm when compared to only 9% patients showing dysphagia in the RT alone arm (55).

There are other studies, which concentrate on intensifying these chemo-RT regimens in an attempt to achieve better tumour control rates, but such studies have reported a feeding-tube dependence rate of about 20% at the end of one year in the experimental regimens (54). Recent evidence has shown that aspiration along with dysphagia is an important sequel of chemo-RT regimens but in many cases is not reported or not given the same importance (56,57).

In any case, patients being treated with RT for any malignancy, the main objective of treatment is to achieve maximum dose conformity and the least dose possible to the surrounding normal structures. With such an aim, it is possible to reduce the subsequent morbidity in patients even with the use of intensive chemo-RT regimens. When we consider dysphagia and aspiration to be important sequel of treatment in head and neck cancers, achieving required dose constraints to the anatomic structures, which are responsible for the same, QOL of such patients can be significantly improved along with achieving the desired local tumour control.

In terms of toxicity, early onset symptoms can be controlled or managed with temporary gastric tube feeding. Chemo-RT regimens or aggressive accelerated RT gained ground and became the preferred treatment of choice with the introduction of concept of “functional preservation” or “organ preservation”. Such an approach has no meaning when the preferred intensive treatment regimens aimed at high tumour control but produce long term persistent toxicity thus depriving a good QOL. Apart from late and persistent dysphagia, intensive treatment regimens with concurrent chemo-RT or accelerated RT are also found associated with late laryngeal edema, chance of aspiration and an increased risk of pneumonia. Recently it has been concluded that late

pharyngeal toxicity is the only hindrance to achieving the best possible control rates. Efforts should be directed towards improving the therapeutic ratios with the help optimal chemo-RT regimen aimed at maximum possible dose conformity.

If such target dose conformity can be achieved and the dose delivered to the anatomic structures responsible for dysphagia and aspiration can be reduced then the incidence and severity of dysphagia in such patients can be considerably reduced. To address and investigate this issue, many recent studies have been initiated. For such an investigation, first step is to identify the anatomic structures whose damage or abnormality cause dysphagia or aspiration. In one such study by *Avraham eisbruch et.al* (58) identified the pharyngeal constrictors (PC) and the glottic and supraglottic larynx (GSL) as the structures whose anatomic structural changes and malfunction cause post therapy dysphagia/aspiration. Once these structures were identified, efforts were made towards implementing modified strategies aiming at reducing the dose to these structures. Few such strategies were based on intensity-modulated radiotherapy (IMRT), namely dysphagia/aspiration-specific IMRT which improved the sparing of these structures thus resulted in reducing the dose delivered to these structures when compared to standard IMRT plan which does not involve giving such dose constraints

(58). However, in any case utmost care should be taken that in an attempt to spare the dysphagia related structures the target tumour volume should not be missed or under-dosed.

1.5 Review of Literature:

1. *Avraham eisbruch et.al.* has done a study aimed at identifying the structures whose anatomic or functional abnormality cause impaired swallowing leading to dysphagia and aspiration. They also studied the feasibility of sparing of such structures using specialized IMRT strategies in which care was taken not to compromise the target tumour volume. A total of 26 patients were taken up for this study. They received concurrent chemo-RT with gemcitabine regimen, an intensive regimen, which is known to be associated with increased incidence of dysphagia related toxicity. To make sure that the morbidity is not regimen specific, 6 patients also received RT with intra-arterial cisplatin. Apart from this, the possibility of sparing of dysphagia and aspiration related structures was explored with the help of modified IMRT strategies (doIMRT) and not compromise on the target volume. The VF abnormalities were noted in both pre and post treatment scenarios along with subjective assessment of dysphagia. This study identified the post-therapy VF abnormalities, which were found to be common to both

the chemotherapy regimens. The abnormalities noted which contributed to a high rate of aspiration were:

- Larynx being elevated
- Impaired laryngeal closure
- Tilting of the epiglottis

This study also helped to identify the anatomical structures by observing the changes in those who's structural or functional abnormality can result in dysphagia and aspiration. These structures were identified as the pharyngeal constrictors (PC) and larynx and supraglottic larynx (GSL). The planning goal was set so that these structures receive a mean dose of about 50Gy by reducing the volume of these structures receiving more than 55Gy. It was concluded that the structures whose anatomical deformity are responsible for causing dysphagia and aspiration to be pharyngeal constrictor muscles (PC), glottic and supra glottic larynx (GSL). When compared to 3DCRT, the use of specialized and optimized IMRT plans were able to spare these structures. The dosimetric goal was achieved with the help of IMRT better than 3DCRT but a clinical validation is required to check whether the dosimetric gains translate into clinical ones.

2. Felix.y.Feng.et.al - have presented initial results of a clinical trial in which intensity-modulated radiotherapy (IMRT) was used to reduce the dose delivered to the swallowing structures whose impairment after chemo-radiation is most likely to cause dysphagia and aspiration, but never compromising the target volume dose. This is a prospective longitudinal study, which included patients of stage I- IV of Nasopharynx and oropharynx. All these patients were treated with definitive chemo IMRT regimen with an aim to spare the dysphagia related structures which include the pharyngeal constrictors (PC), glottic and supra glottic larynx (GSL). Since the retropharyngeal nodes are in close approximation to the constrictors, lateral nodes were considered to be high risk but not the medial RP nodes. Evaluation of dysphagia was done using video-fluoroscopic images and patient reported and observed reported scores were considered. The relation between the dose received by these structures and the structural changes observed in these structures were compared from before therapy to 3 months after therapy.

There was a significant change noted in videofluoroscopy-based aspirations when these changes observed were compared to the mean doses received by these structures. The mean doses as well as the partial

volumes of these structures (PC and GSL) receiving 50-65Gy were significantly correlated when compared to the videofluoroscopy-based aspirations; the most significant correlations were found to be with the superior pharyngeal constrictor ($p = 0.005$). It was also found that in all the patients who had aspirations, the mean dose to the pharyngeal constrictors was >60 Gy or volume of PC receiving 65 Gy was more than 50%, and the volume of GSL receiving more than 50Gy was more than 50% as well.

The mean PC and GSL doses correlated well with reduced laryngeal elevation and epiglottic inversion ($p < 0.01$). All the patients with strictures (3) had PC V70 $>50\%$. Patient related dysphagia correlated with mean doses to the PC. Such dose-volume relationships provide optimized IMRT goals and increase our interest to put in increased efforts to reduce doses to swallowing and thereby reducing the incidence of dysphagia and aspiration.

3) *Jaiprakash Agarwal et al.* - This study was done to objectively assess swallowing and the factors affecting it in patients with squamous cell carcinoma of head and neck (HNSCC) who have been treated with definitive chemo-RT regimen and a curative intent. A cohort of 47

patients with loco-regionally advanced (T1–4, N0–3) HNSCC who were treated with definitive CRT was taken for this study. The swallowing was assessed objectively with the help of scoring of MBS in pre-CRT as well as the subsequent follow-ups. The score was done using the penetration–aspiration scale (PAS). Any abnormality in swallowing was weighed in terms of severity and incidence of penetration-aspiration, residue in pharynx, change in posture and regurgitation.

In the pre-CT assessment 9 patients showed aspiration where as at 6 months post CRT this was found to increase to 11 patients (19% to 29%). In the same way when pre-CT assessment was compared to 6 months post CT residual material in pharynx changed from 11 patients to 13 patients (23% to 29%) postural change was found to be increasing from 10(21%) to 12(32%) patients and finally regurgitation was found to be in patients 5 patients and 10 patients (10% to 26%). When PAS scores were observed the proportion of patients with high PAS scores (3-7) also increased from 27%V to 37% from baseline to 6 months post CRT. The patients who had low PAS scores at baseline, were found to have additional impairment of swallowing function at 2 months and 6 months post CRT follow up study. In post CRT study a high proportion of patients were found to have impairment in the residue and aspiration groups. The consistency of barium, thin and thick barium were found to

influence the rate of aspiration or residue. Thick barium had higher function of residue and thin barium showed a higher function with aspiration. Patients who had pre CRT poor swallowing function, with hypo pharyngeal primary and large volume disease were found to have worse objective swallowing proven with the help low PAS scores to baseline. It was concluded that there is statistically significant impairment in objective swallowing in all aspects of swallowing i.e, aspiration, residue, regurgitation and postural change and found to be the most in aspiration and residue domain. The patterns of objective swallowing dysfunction in patients with HNSCC being treated with CRT were made clear in this study.

AIM

This is a study aimed at assessing the clinical advantages achieved with the help of different IMRT strategies (standard IMRT and dysphagia/aspiration-specific IMRT). This is a prospective study which mainly focuses on the clinical advantages of reducing the dose received by the swallowing structures, pharyngeal constrictors (PC), glottic and supraglottic larynx (GSL) and esophagus, and the corresponding changes in the subjective and objective swallowing dysfunction and aspiration from before the start of treatment to 3 months after end of treatment. It focuses on reducing the volume of these structures receiving doses more than 50Gy but also emphasize on the importance of compromising the target volume. The primary end point of this study is to analyze dysphagia in patients treated with sparing of swallowing structures and secondary end point is to compare this to retrospectively analyzed patients without constraints for dysphagia structures.

MATERIAL AND METHODS

This is a prospective, longitudinal study among patients being treated with chemo-IMRT for squamous cell carcinoma of head and neck who were being treated with radical chemo-RT with a curative intent. The main objective of this study is to assess the dysphagia resulting from treatment.

In order to avoid tumor-related effects on the endpoints of this study, it was decided to exclude patients with laryngeal or hypo-pharyngeal cancer because such cases have high incidence of pre-treatment pre-existing swallowing dysfunction and aspiration (disease-related) (59). Thus, the disease related factor was excluded to study the effects on treatment related dysphagia only.

Inclusion Criteria

- Cancer of Nasopharynx and Oropharynx
- Stage 3 and 4(T2-T4, N+)
- Histology of squamous cell carcinoma, poorly diff carcinoma and NPC
- All ages 16 – 70yrs
- ECOG PS \leq 2

Exclusion Criteria

- Hypopharynx and laryngeal cancers
- History of previous neck irradiation
- Patients receiving only radiation

Radiotherapy

The principles of target selection and IMRT planning followed are as per the general consensus of target delineation in head and neck cancers (60,61). In case of Nasopharynx or oropharynx the whole neck needs to be covered in the target volume. When using two opposing lateral fields to treat the primary and neck, the coverage of lower neck becomes an issue. There are two ways in which that can be achieved. One, by including the whole neck in the IMRT plan and delineating the nodal GTV and CTV and the other way is to add an anterior lower neck field. With a lower neck anterior field, the deeper targets will be under dosed and for the same reason we have avoided using an anterior field.

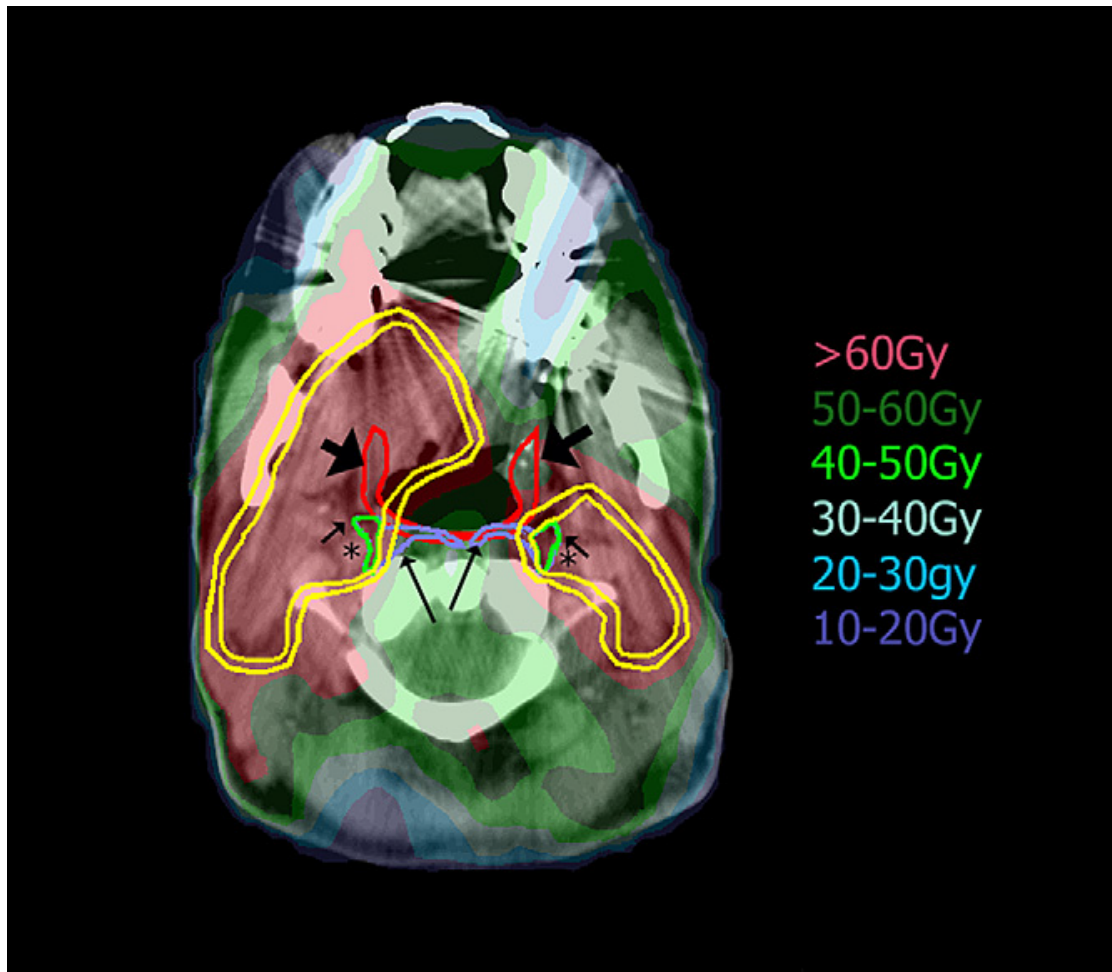
Delineation of retropharyngeal (RP) nodes was given due importance in this study. These nodes are defined as targets for all nasopharyngeal and almost all oropharyngeal cases and especially in cases with other clinically involved nodes.

The retropharyngeal nodes are bounded anteriorly by the pharyngeal constrictors and pre-vertebral fascia covers posteriorly, superiorly the extent is up to the base of skull and up to the level of C3 cervical vertebra inferiorly (62). The retroperitoneal nodes are divided into two groups, lateral retropharyngeal and the medial retropharyngeal nodes. The lateral nodes are located medial to the carotid arteries but lateral to the longus coli and capitis muscles. The medial nodes are present along with the lymphatics near the midline. For the purpose of allowing sparing of the pharyngeal constrictors, the lateral nodes alone were considered high risk for nodal metastases, as they are known to be in all head and neck cancers and especially in nasopharyngeal cancers (63-73). The medial RP nodes were not included as targets unless there was a gross radiological involvement of the lateral RP nodes, as they were found to be rarely involved. The medial RP nodes were not included in the nodal target volume as they were found to be rarely involved. These nodes were considered to be at high risk or included in the target volume only if there were found to be grossly involved radiologically.

While defining target volumes, the planning target volumes (PTVs) were created using a uniform margin of about 0.5cm from the clinical target volume (CTV) which accounts for the daily setup errors which

were monitored based on weekly imaging (daily imaging not feasible in current set-up) and not allowed to be anything beyond 1-1.5mm.

Contouring of the swallowing structures includes pharyngeal constrictors (PC), glottic – supraglottic larynx (GSL) and esophagus. The contouring of these structures was done based on anatomic atlases. The PC was contoured as a single organ starting at the level of pterygoid plates superiorly and inferiorly up to the level of lower border of cricoid cartilage. The PCs are divided into superior, middle and inferior constrictors for the purpose of analysis. The superior constrictors begin from base of skull up to the upper edge of hyoid bone. The middle constrictors extends through the superior edge of hyoid bone to inferior edge and the inferior PC is from the hyoid up to the inferior edge of cricoid cartilage. In the same way, the glottic and supraglottic larynx was contoured as one single organ starting at the level of epiglottis (according to the latest TNM classification, epiglottis is included as a sub site of supra glottic larynx) up to the lower border of cricoid cartilage, which anatomically marks the beginning of the upper esophagus i.e. the cricopharyngeus muscle. The esophagus was contoured from the inferior edge of cricoid up to the level of caudal extent of the lower neck fields.



Clinical target volumes (CTV) with PTVs in respect to RP nodes (red) and PCs – yellow
 CTVs of the lateral RP nodes – green
 Retropharyngeal space medial to carotids – asterisks
 CTVs do not include the medial RP nodes – marked by blue and long arrows.

The dose prescription includes all the targets delineated in high risk PTV to receive TD-60-66Gy at 200cGy DD/fraction and TD 50-55Gy to sub clinical/low risk PTV. With the help of in house planning systems (VARIAN), inverse IMRT plans were analysed and executed once target dose homogeneity is achieved (74). An optimized IMRT plan was thus

generated (study IMRT) which included the dose given to the delineated PTVs as per the RTOG protocol along with an optimization goal to try and constraint the dose to the swallowing structures. The swallowing structures contoured were given a dosimetric goal of maximal dose of 50Gy if and when they are contoured outside the PTV. No compromise to the primary target PTV was allowed while sparing these structures and for achieving optimum dosimetric goals, the structures that outside the PTV only were spared.

In all patients, the prescription dose to the targets was considered as high priority and other critical organ dosimetric constraints were considered to be secondary except for maximal spinal cord dose. The optimized IMRT strategy for sparing of the swallowing structures was implemented by subtracting these structures from within the PTV and for the purpose of the study these dose prescriptions were considered to be clinically significant. For the whole structures and the parts that overlapped the PTVs, DVH analyses were performed and reported.

Dose specifications and constraints used for two IMRT strategies

1. *Standard IMRT*

Targets

- PTV60 for the radiological gross disease; prescribed dose 60Gy in 30 fractions

Noninvolved tissues and organs

- 2/3 of the glottic larynx should receive $>50\text{Gy}$
- Maximal dose to brain stem 54Gy
- Maximal dose to spinal cord 45Gy
- Maximal dose to mandible 70Gy

All the non-specific tissues outside PTVs: $<1\%$ to receive $<110\%$ of

PTV60 dose

In at least one parotid gland, mean dose $<26\text{Gy}$ or $<50\%$ receive $<30\text{Gy}$

2. *Study IMRT*

The dose specifications and constraints given are the same as that for Standard IMRT.

In addition, the volume of dysphagia and aspiration related structures receiving $>50\text{Gy}$ were reduced as much as possible without compromising target PTV.

(Abbreviations: IMRT - intensity-modulated radiotherapy; Standard IMRT - standard IMRT; PTV - planning target volume; PTV66=66Gy to PTV of gross disease; RTOG - Radiation Therapy Oncology Group)

Chemotherapy

- Oropharynx - Oropharynx- weekly cisplatin ($40\text{mg}/\text{m}^2$) along with RT for minimum of 5 weeks.
- Nasopharynx- 3 cycles of cisplatin ($70\text{mg}/\text{m}^2$) once in 21 days along with RT followed by 3 cycles of cisplatin ($70\text{mg}/\text{m}^2$) +5FU (IV bolus, 500mg from d1-d3) every 21 days, adjuvant therapy.

Supportive care

- Anti-emetics and adequate hydration both before and after chemotherapy was delivered following standard of care.
- Among patients having dysphagia and malnourishment, nasogastric tube intubation was initiated.

Evaluation of Dysphagia

The evaluation of dysphagia and swallowing dysfunction in respect to aspiration and penetration was done from before therapy to 3 months after therapy both subjectively (patient-reported) as well as objectively

(observed). The primary end point of this study is to analyze the changes and the incidence of dysphagia in relation to the DVH of these structures.

The objective or observed evaluation of swallowing was done using barium swallow studies using both thick and thin consistencies. An interventional radiologist was present to analyze the dysphagia and aspiration using PAS (Table) (75).

For evaluation, the movement of the barium was observed in real time and in slow motion. Frame-by-frame analysis was required in order to evaluate the function of oral, pharyngeal and laryngeal and UES. Swallowing dysfunction was defined in terms of either the incidence or severity of penetration–aspiration, residue in pharynx, swallowing regurgitation, and change in posture during swallow. When any portion of the bolus which is entering the laryngeal vestibule at the level of vocal cords but not passing below the vocal cords is known as Penetration. In a similar way aspiration is when the penetrated bolus passes below the level of the true vocal folds and finally enters the subglottic region. Portion of the swallowed bolus, which is left behind in the pharyngeal spaces such as valleculae and pyriform sinuses is nothing but the Pharyngeal residue. Barium swallow was repeated using thin and thick barium.

Grade	Observation	Interpretation
1	Contrast agent does not enter the airway	Normal
2	Contrast agent enters the airway, but remains above the vocal folds; no residue	
3	Contrast agent remains above the vocal folds; visible residue	Penetration
4	Contrast agent contacts the vocal folds; no residue	
5	Contrast agent contacts the vocal folds; visible residue	
6	Contrast agent passes the glottis; no subglottic residue	Aspiration
7	Contrast agent passes the glottis; visible subglottic residue despite patient response	
8	Contrast passes the glottis; visible subglottic residue, absent patient response	

PAS on MBS - Interpretation: 1-2 = Normal; 3-6 = Penetration; 7-8 = Aspiration

Patient-reported dysphagia was assessed with two validated head and-neck cancer–related quality-of-life questionnaires given to patients before therapy and 3 months after the completion of therapy. They included the Head and Neck Quality of Life (HNQOL) instrument (76) and the University of Washington Head and Neck-related Quality-of-Life (UWQOL) instrument (77).

HNQOL – questionnaire contains two questions related to dysphagia

- “How much are you bothered by swallowing liquids?”
- “How much are you bothered by swallowing solids?”

Each having five possible answers –

- “Not at all”
- “Slightly”
- “Moderately”
- “A lot”
- “Extremely”

UWQOL - Contains one swallowing question with five possible answers

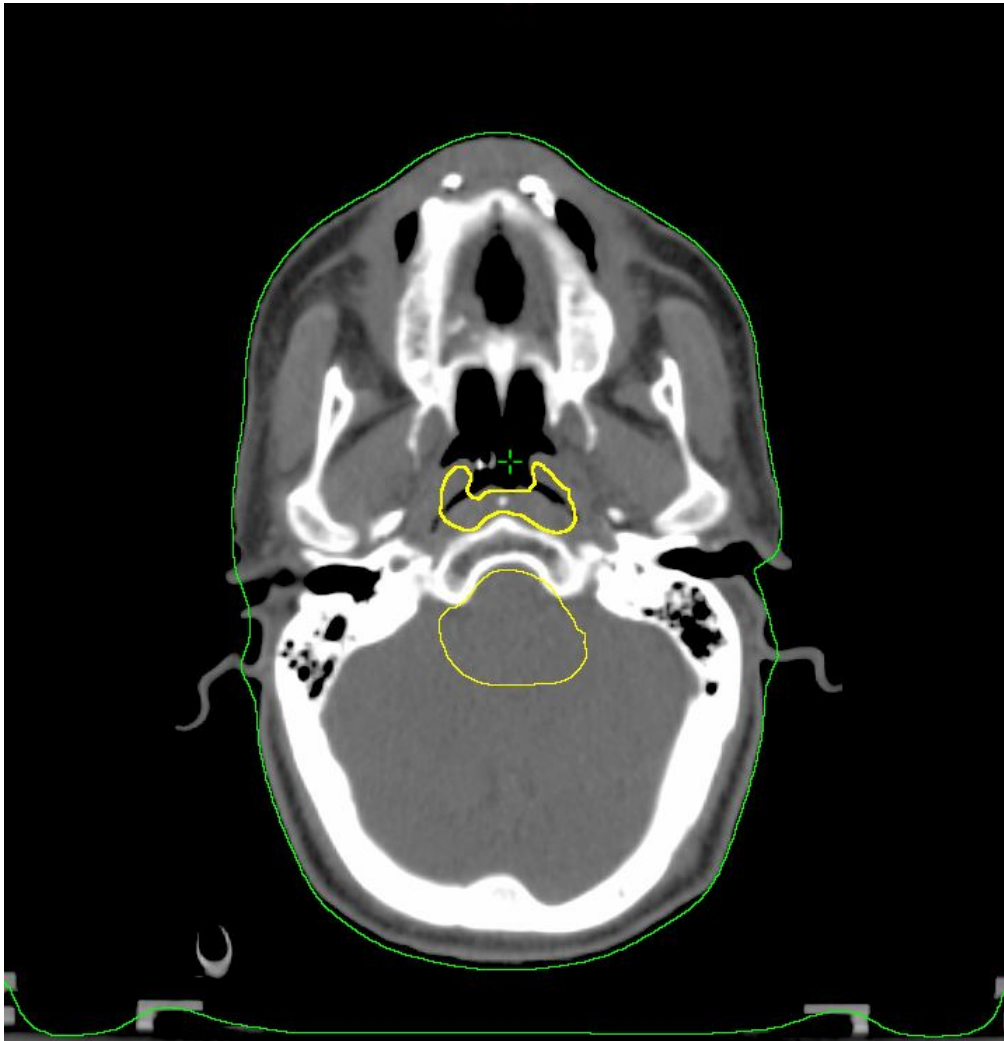
- “I swallow normally”
- “I cannot swallow certain solid food”
- “I can only swallow soft food”
- “I can only swallow liquid foods”
- “I cannot swallow”

Statistical Analysis

The dose volume effect relationships of all the dysphagia outcome measures and dose values were modeled using multiple regression analyses, with the score of dysphagia using PAS scoring system, measure from before treatment to 3 months after therapy as the dependent variable. Statistical significance was determined at $p \leq 0.05$ (two-tailed).

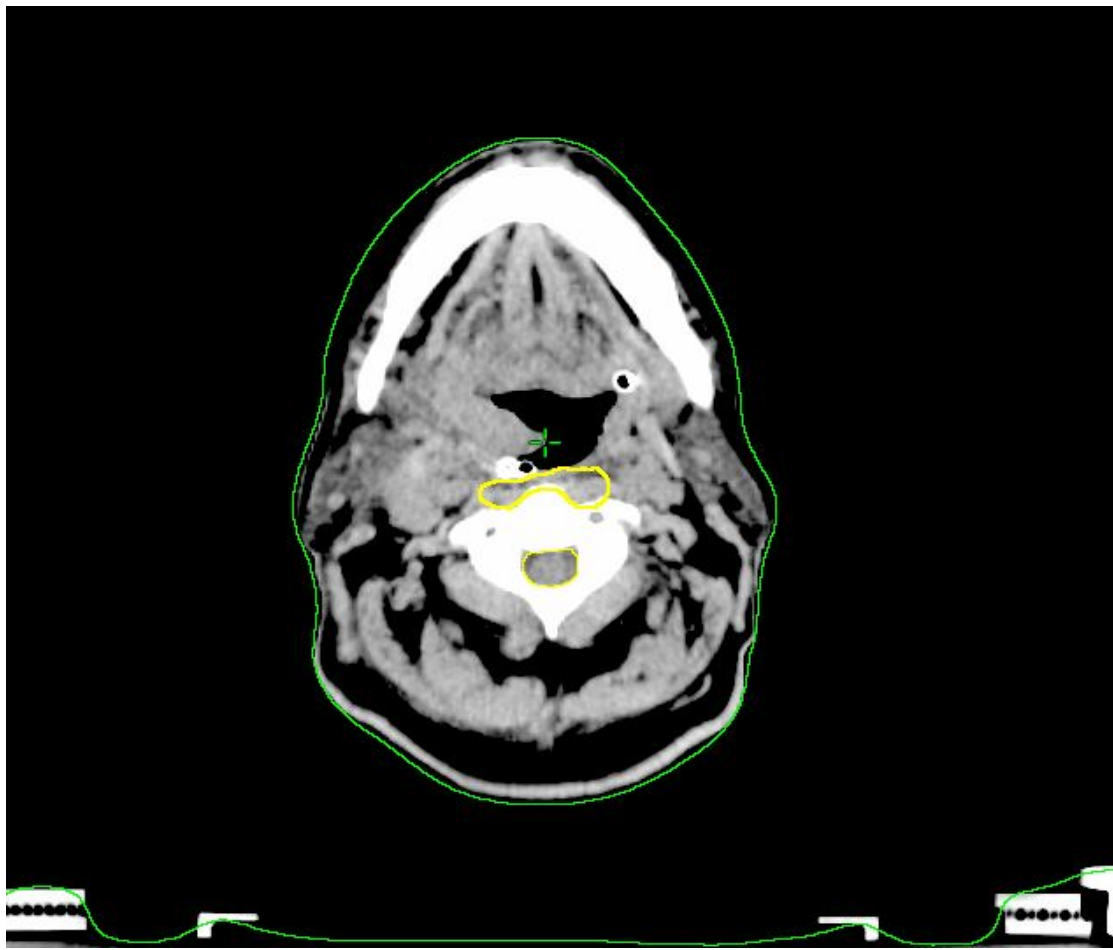
Contouring of superior pharyngeal constrictors

The contouring of the superior pharyngeal constrictors begins at the level of pterygoid plates. When the imaging modality used is CT scan, delineating the PC becomes difficult. The area near the midline, medial to the carotids, longus coli and capitis muscle is considered to be the PC. As mentioned earlier, the lateral RP nodes alone are considered to be high risk and accordingly, when contouring is done medial to the capitis muscle it will not include the lateral RP nodes in the PC contour.



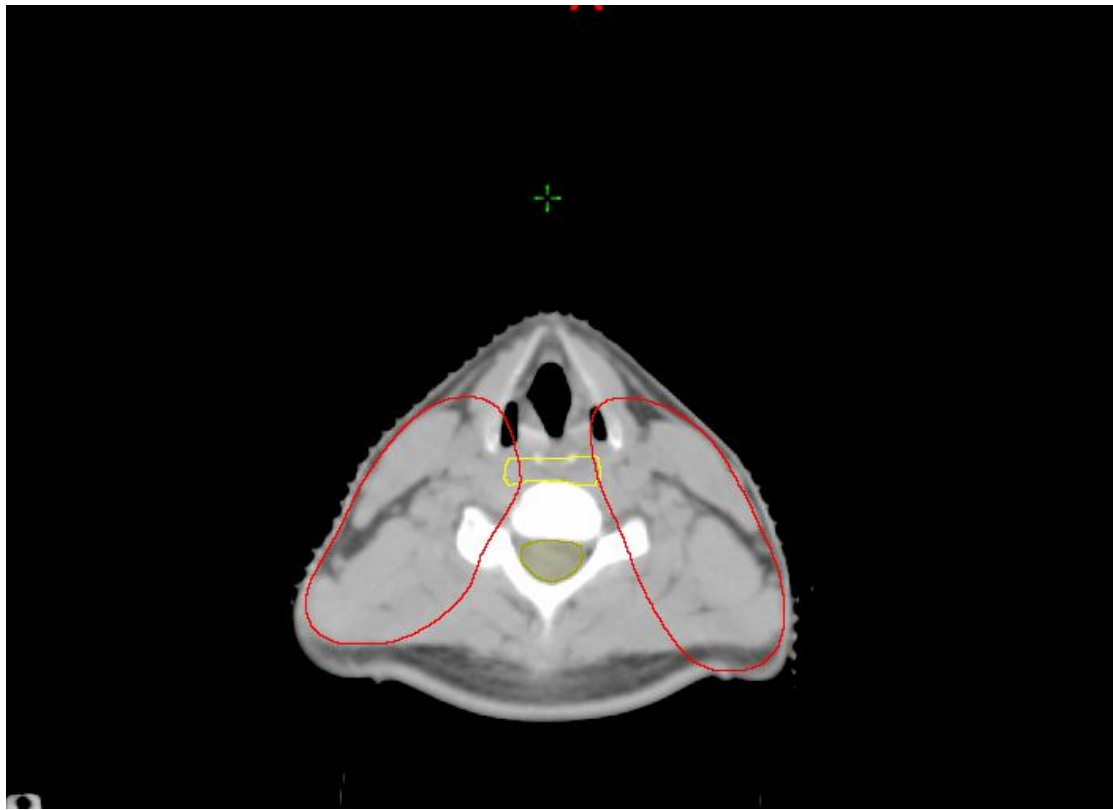
Contouring of middle pharyngeal constrictors

The contouring of the middle pharyngeal constrictor begins at the level of the superior edge of the hyoid bone and extends through it up to the lower edge of the hyoid. This part of the PC is the smallest of the three sub divisions. Delineation the middle PC with respect to the RP nodes is the same when compared to the superior PC i.e. medial to the carotids. The involvement of the medial RP nodes is very rare especially in case of an oropharyngeal carcinoma.

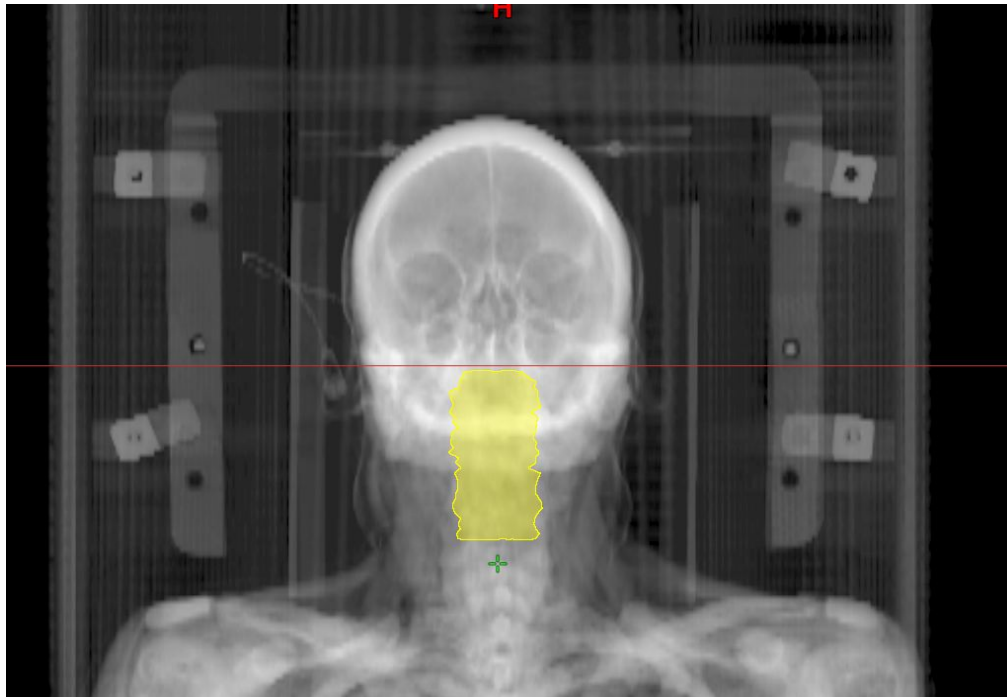


Contouring of the inferior pharyngeal constrictor

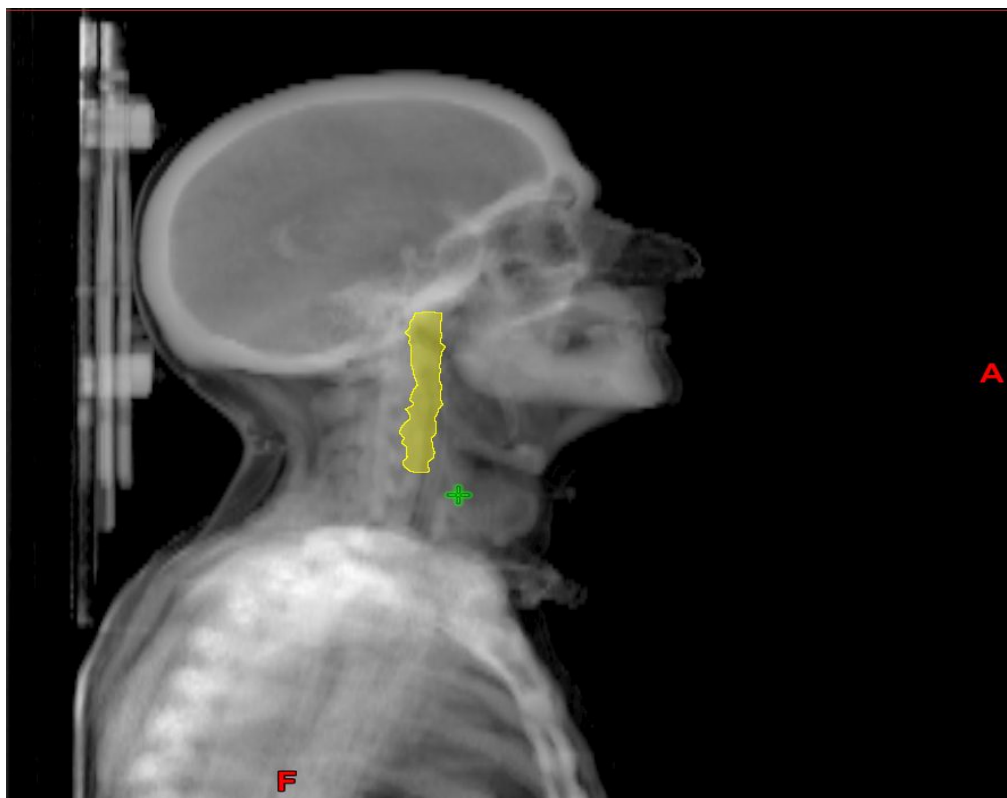
The inferior pharyngeal constrictor is contoured from the level of lower border of hyoid bone to the lower border of the cricoid cartilage. In such a case, the constrictor is found posterior to the larynx along the posterior pharyngeal wall. When contouring the GSL, there is a probability of overlap of contours between the three i.e. PC, GSL and the corresponding target volumes.



Topographic view of the contouring of the pharyngeal constrictors



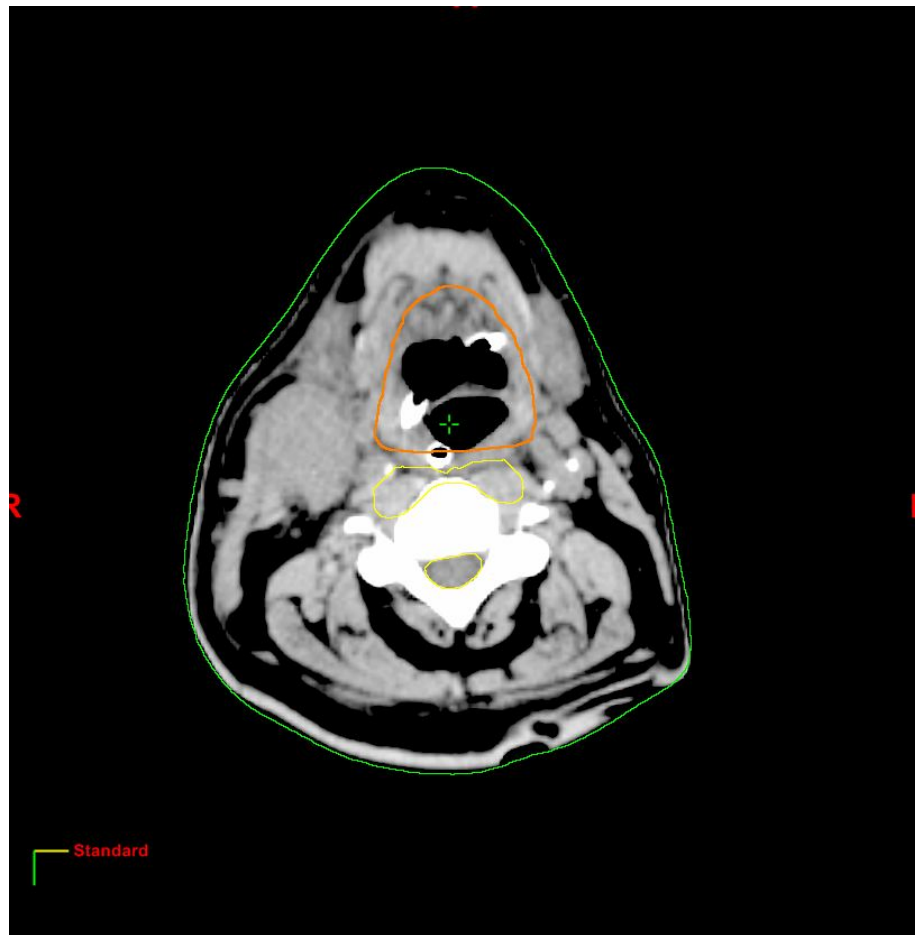
AP VIEW



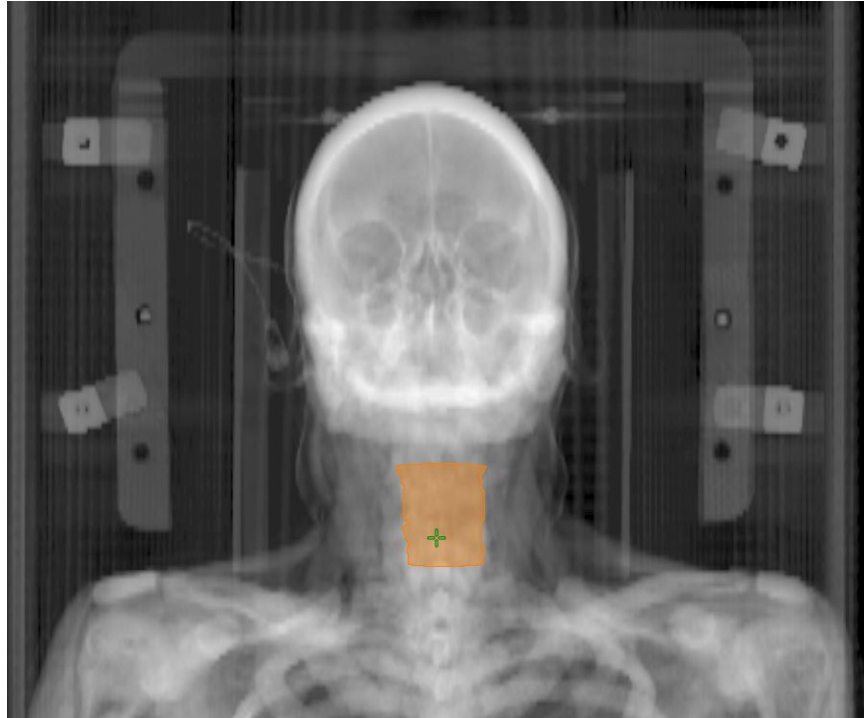
**LATERAL
VIEW**

Contouring of GSL beginning at the level of epiglottis

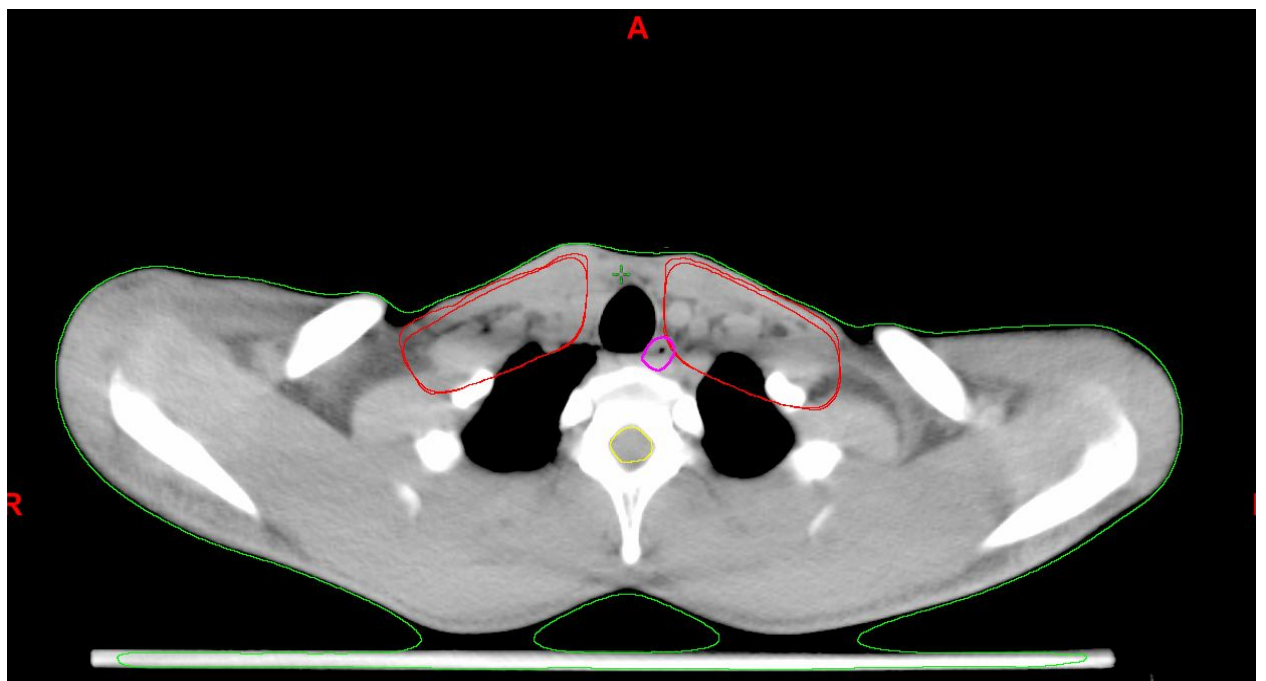
The glottic and supra glottic larynx are also contoured as a single organ as in the case of pharyngeal constrictors. We have considered beginning the delineation of the supra-glottic larynx at the level of epiglottis since its incorporation into the supra glottic larynx as per the AJCC staging.



Topographic view of the contouring of GSL

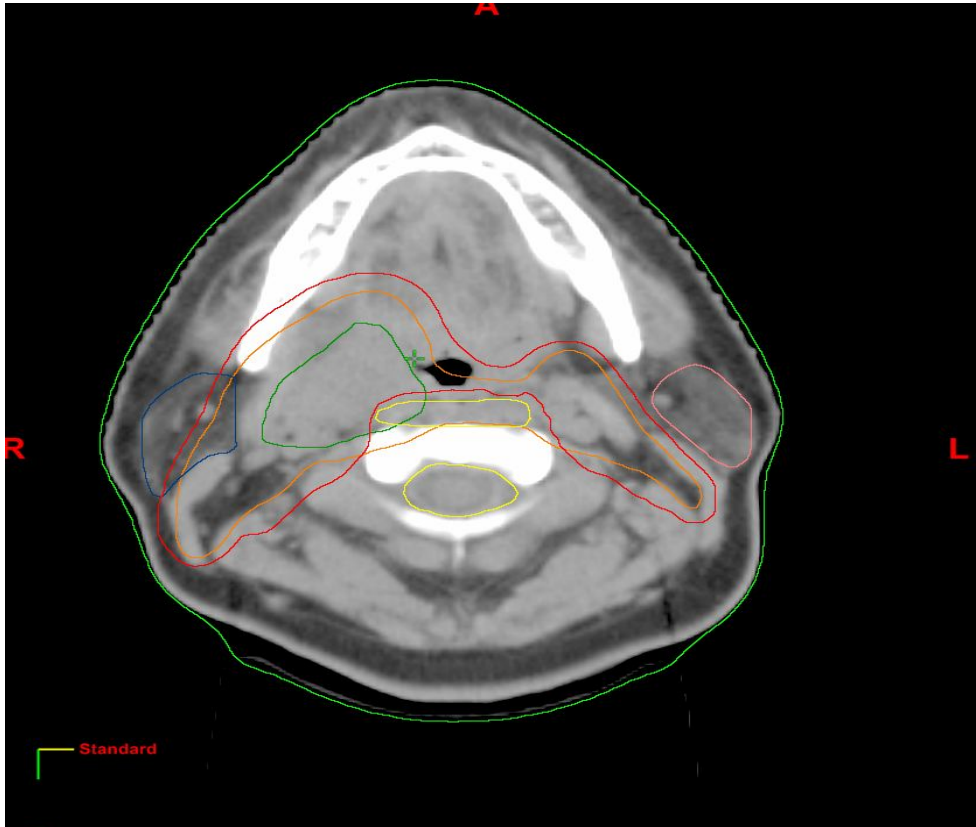


Contouring of the esophagus

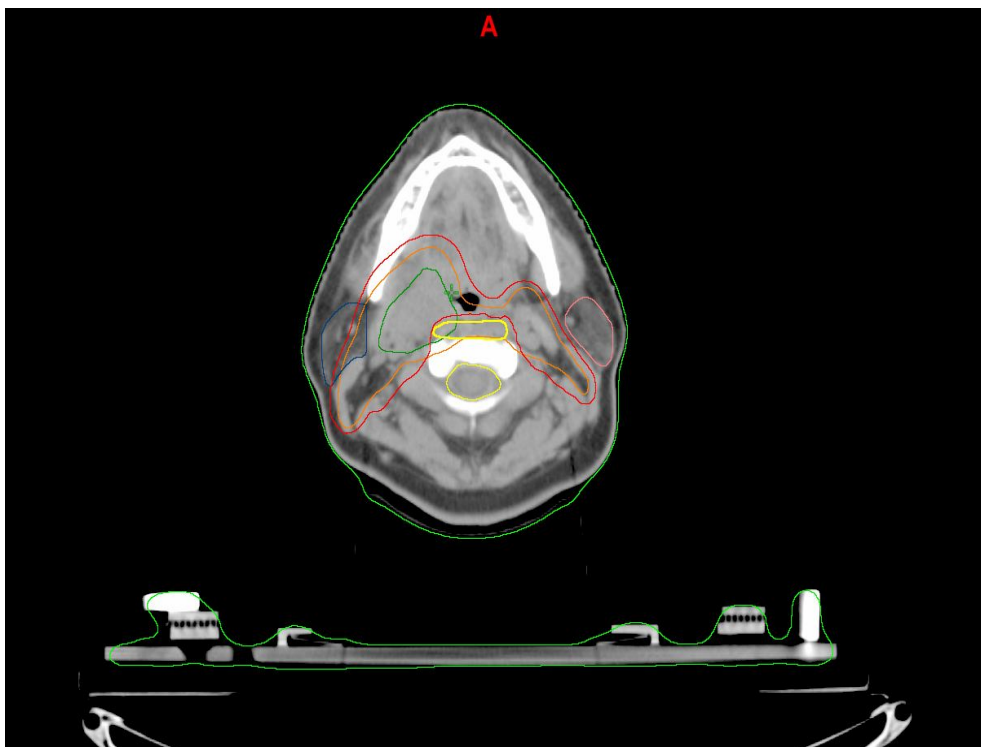


Target Delineation

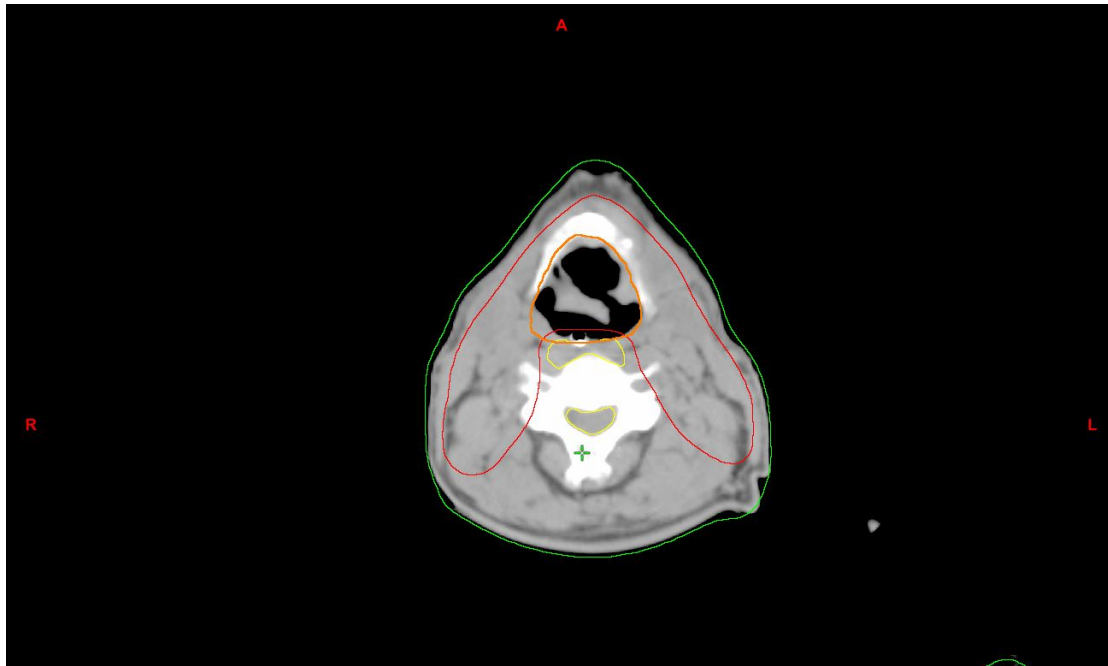
Delineating the Gross tumour volume (GTV), Clinical target volume (CTV) and the Planning target volume (PTV) is an essential part of sparing of swallowing structures. Target delineation is essential since it defines the volume of each of the swallowing structures receiving the prescribed dose. Reducing the relative volume of these structures receiving total prescribed dose is the optimization goal. The image shows the entire target volume delineated with respect to sparing of PC and both the parotids. It can be noted that the volume of PC contoured comes within the GTV, CTV as well as PTV and so does the ipsilateral parotid. In such a case, any reduction in the PTV might result in missing or under dosing the PTV. Thus, the total volume of the PC and parotid in such cases will receive the entire prescribed dose of the PTV60 and a constraint becomes impossible. In case of oropharynx and Nasopharynx as in the case of this study, the superior constrictor and middle constrictor constraints become an issue as it is in the close proximity of the PTV. This is the reason why the optimization goal for this study is the maximum reduction in the volume of these structures receiving 50Gy rather than keeping the mean dose of total volume under 50Gy, which will result in compromising the target and should be avoided in all cases.



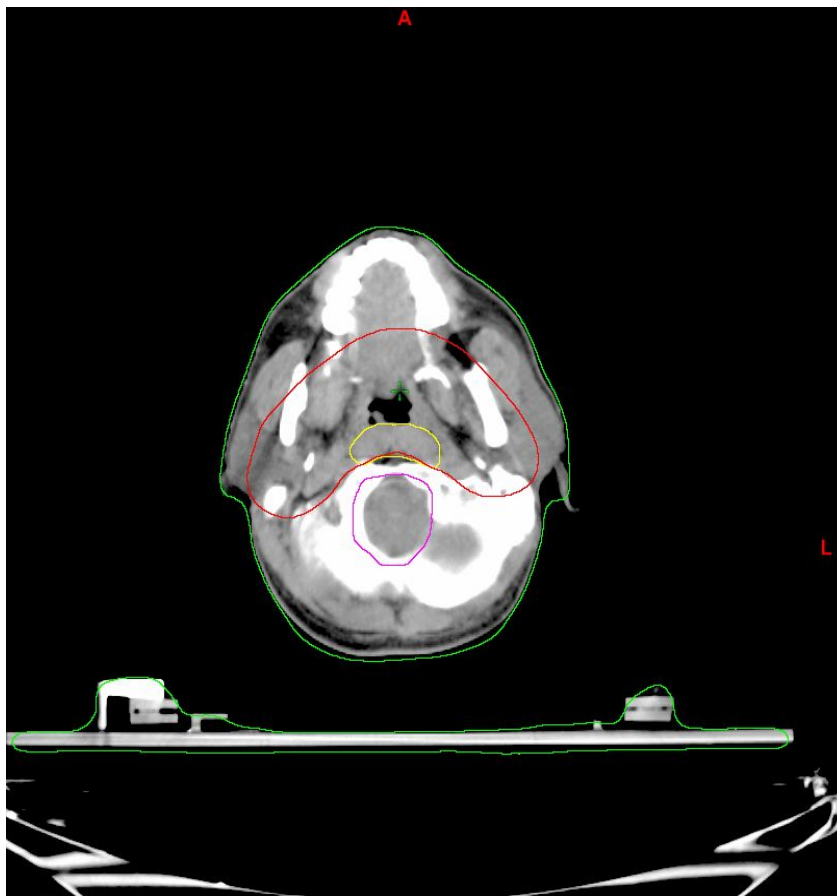
Target delineation with PC and parotid contour at the level of hyoid



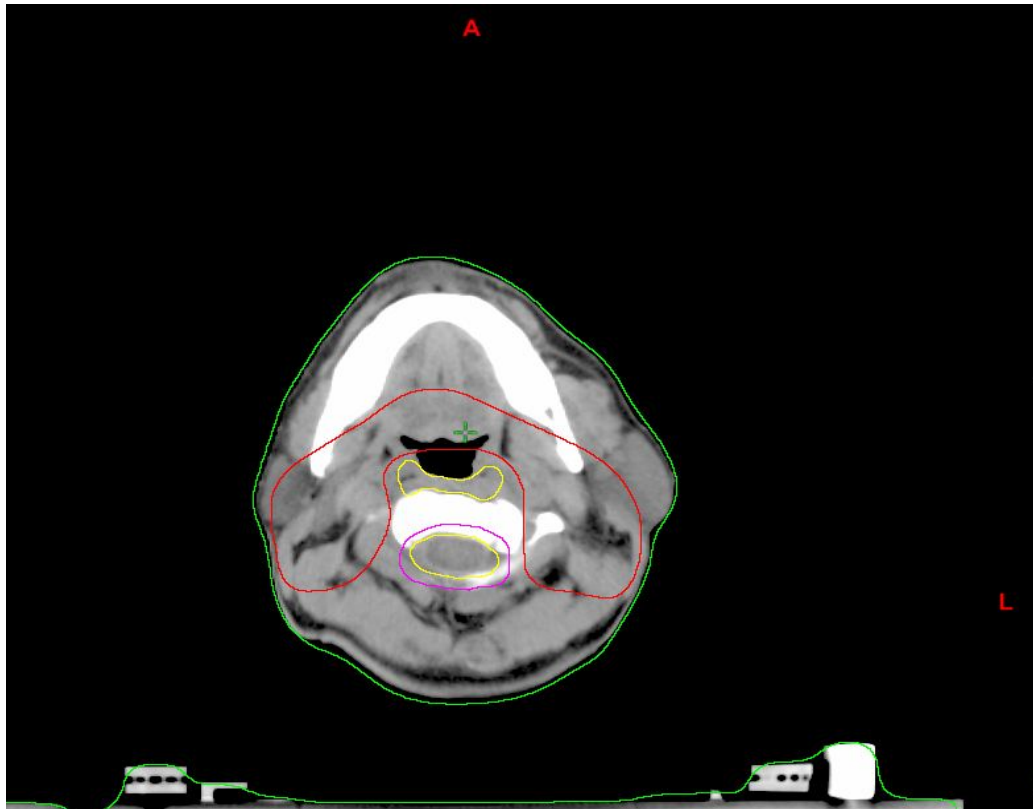
Case of oropharynx (bulky) – sparing of GSL not feasible



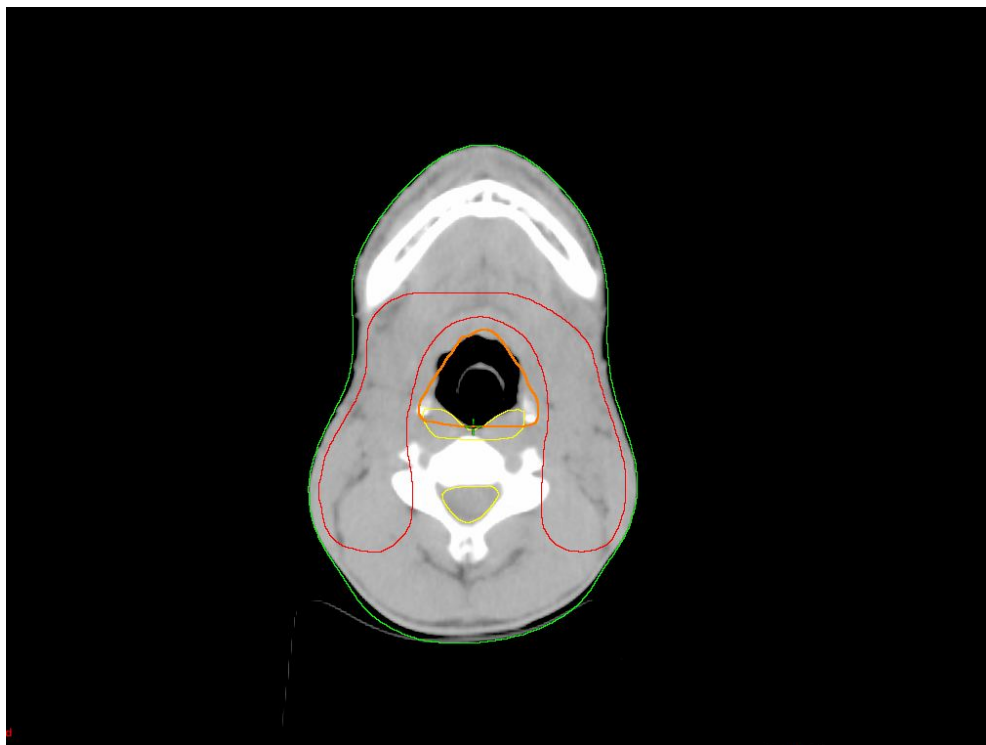
Case of bulky Nasopharynx – superior PC sparing not possible



Sparing of the middle PC in a case of early stage of oropharynx



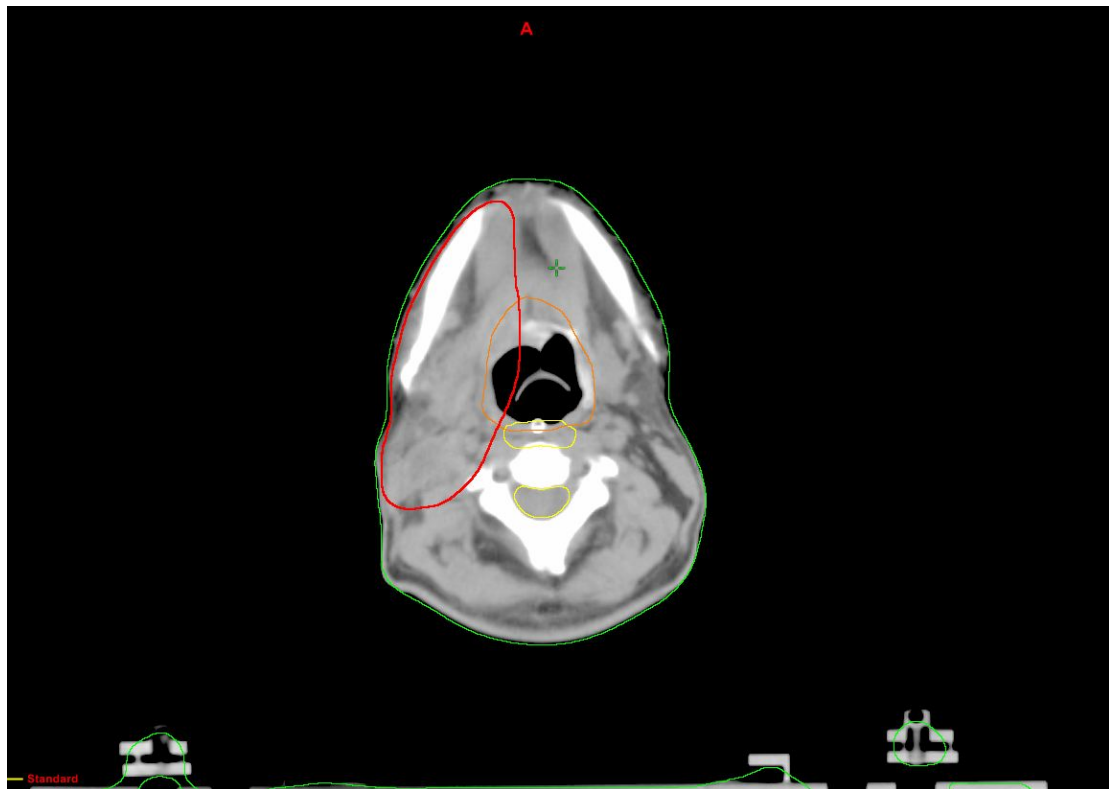
Early stage disease where sparing the PC and GSL is feasible



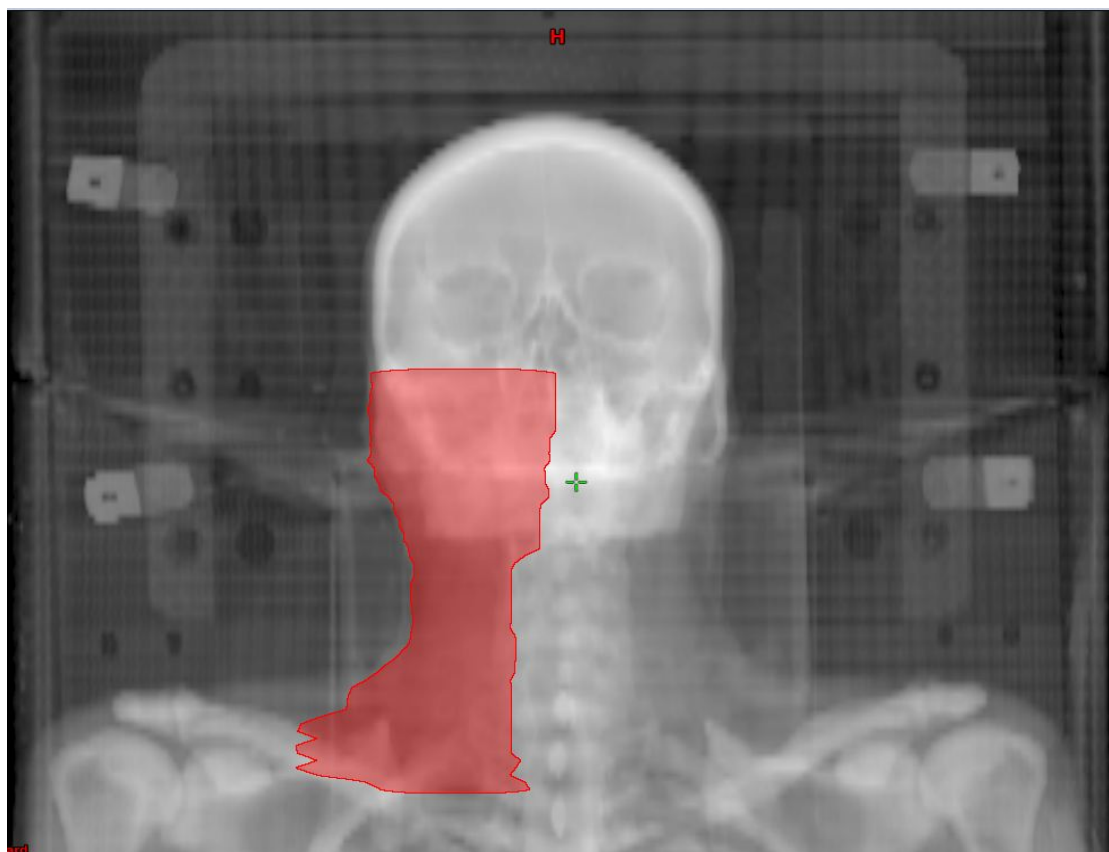
Unilateral PTV Vs Bilateral PTV:

Target delineation in the neck depends on the extent and stage of the primary. In early stage, well-lateralized disease, the recommendation is to treat only the ipsilateral neck. In such a case, the morbidity with respect to dysphagia, skin reactions can be kept at minimum. The volume of PC and GSL receiving PTV60 also is minimal. Whereas in cases where bilateral neck has to be treated i.e. bulky disease or locally advanced disease or bilateral neck node involvement, the sparing of PC and GSL becomes a little challenging. In order to facilitate this, an alternative is to split the PTV/CTV into two, one for each side of the neck and thus considerably reducing the volume of the GSL and PC receiving more than 50Gy. This may not be feasible in all cases i.e. with bulky nodal disease or multiple bilateral nodes where extra precaution is needed so that any of the target volumes are not compromised. There are different ways in which the neck field can be planned. It can be delineated as a part of whole neck PTV in which case sparing of normal tissue becomes an issue except when IMRT is used. The alternative is to split the PTV for the neck as mentioned earlier and finally to use an anterior lower neck field. Anterior lower neck field is the least feasible option with respect to getting adequate dosage to the deeper lying targets.

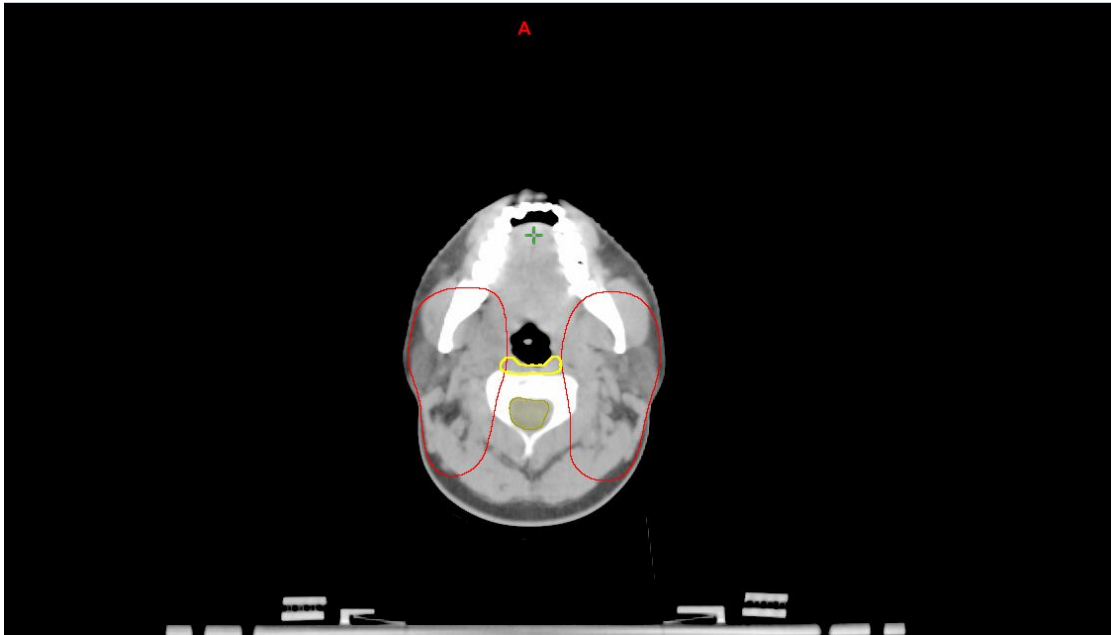
Unilateral PTV with respect to GSL and PC



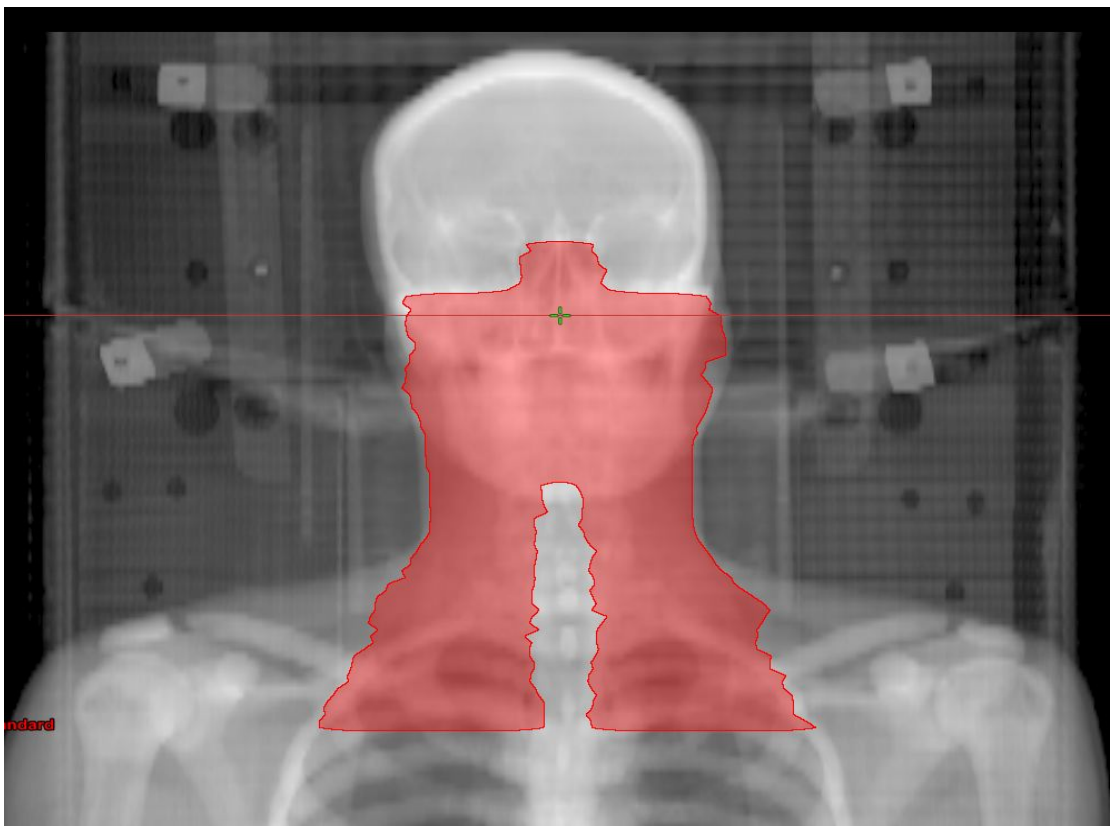
Topographic view of Unilateral PTV



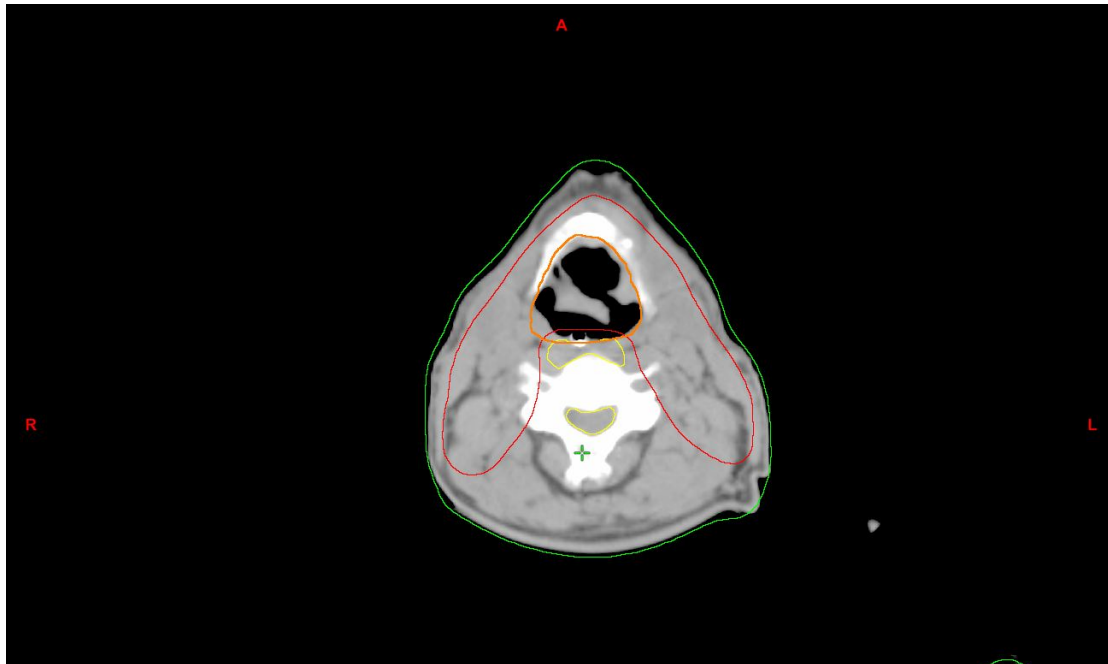
Target delineation in neck – two separate PTVs for bilateral neck



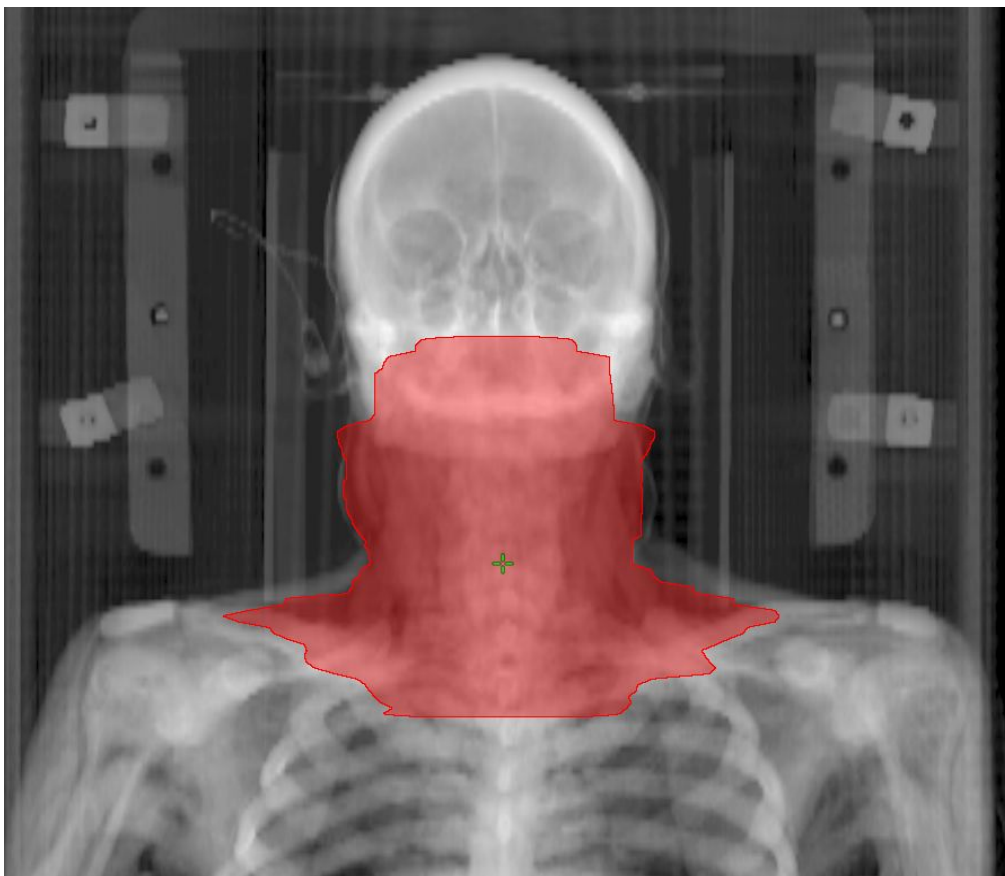
Topographic view of two separate PTVs for either side neck



Target delineation in neck – single PTV for whole neck



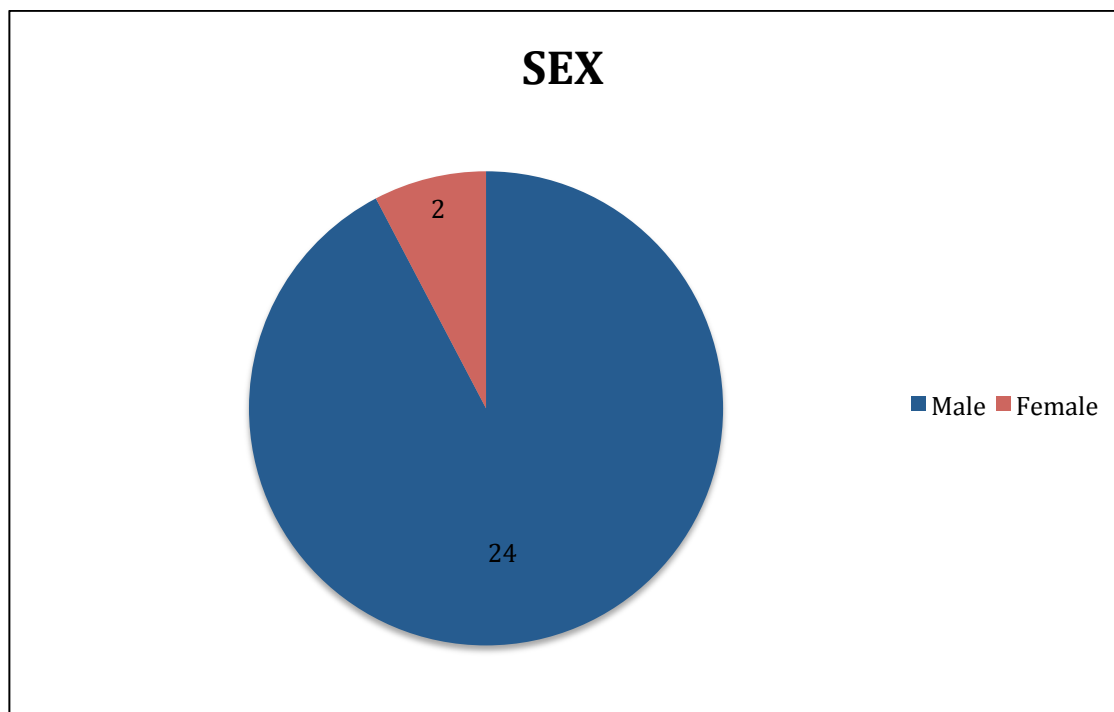
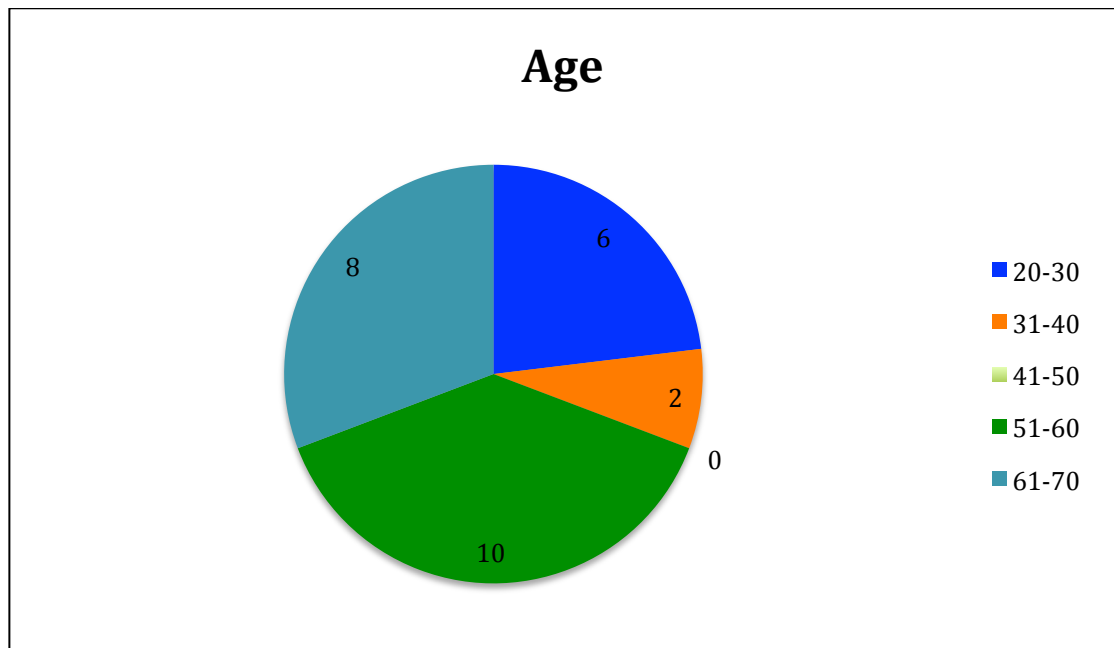
Topographic view of single neck PTV



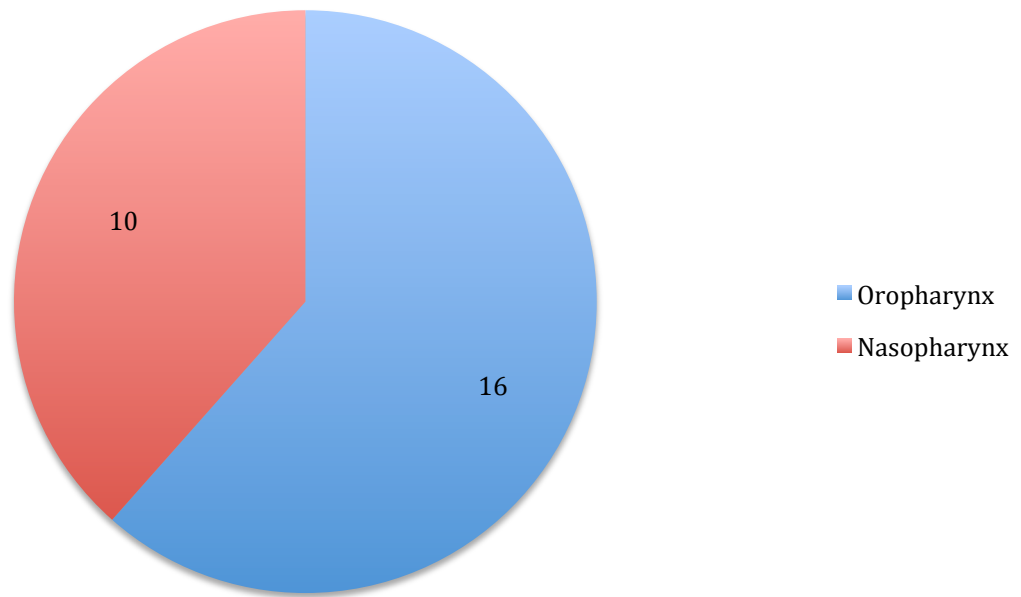
RESULTS

Patient characteristics:

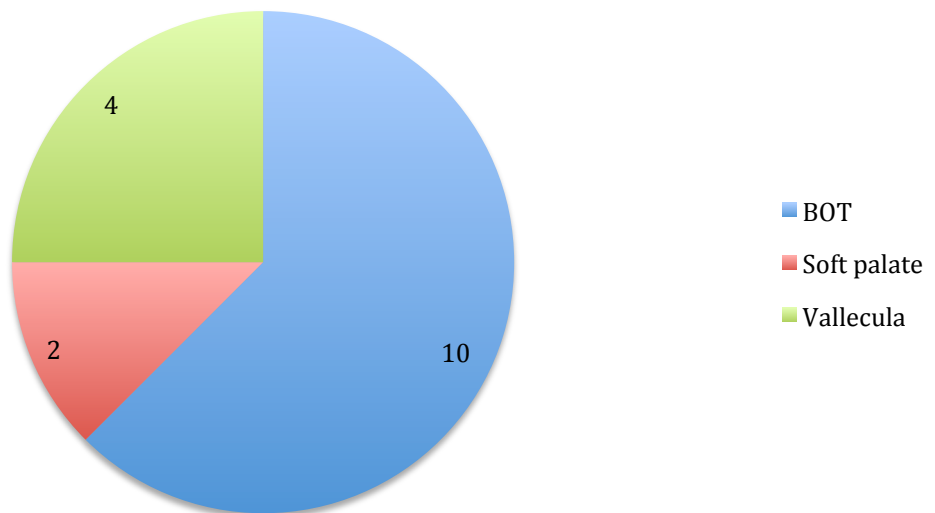
A total of 30 patients were considered for this study. 26 of these patients were treated with concurrent chemo-radiation and included in the study. All are patients of either oropharyngeal or nasopharyngeal carcinoma. Out of which 16 patients were oropharyngeal and 10 patients were Nasopharyngeal carcinomas. Male to female ratio in our study is 12:1. The mean age of these patients were 50yrs. The mean age of patients with oropharyngeal carcinoma is 61yrs and that of nasopharyngeal carcinoma was 34yrs. 6 (23%) out of 26 patients received RT alone and 20 (77%) patients received the protocol concurrent chemo-radiation with weekly or 3 weekly CDDP and those with nasopharyngeal carcinoma also received the full course of adjuvant treatment with 3 weekly cisplatin and 5-FU. Out of the 16 patients with oropharyngeal carcinoma, 60% of the patients had base of tongue as their primary and 5% patients soft palate. 90% of the patients were found to be in locally advanced stage i.e. stage III and stage IVA and 3 (2 from oropharynx and 1 in Nasopharynx) patients were in early stage-II. All the characteristics of the patients and tumours are detailed in with pie charts.



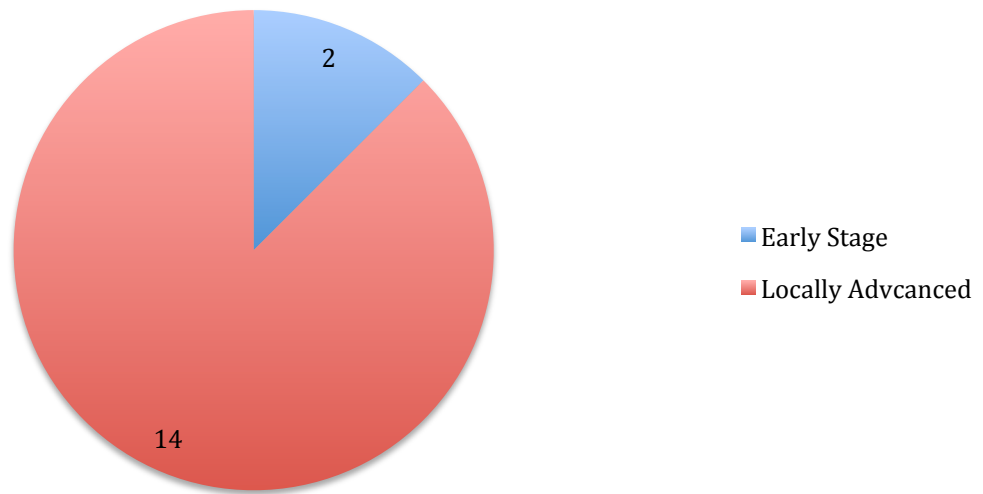
Site of Primary



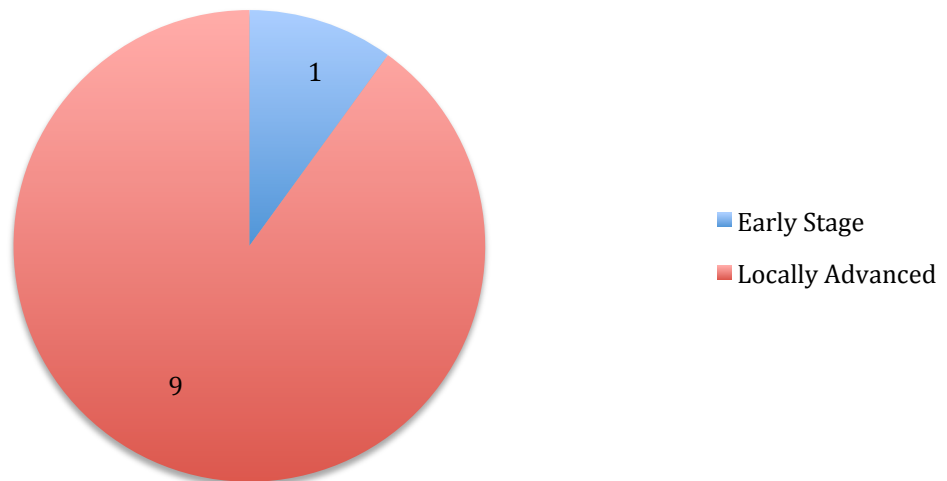
Sub site



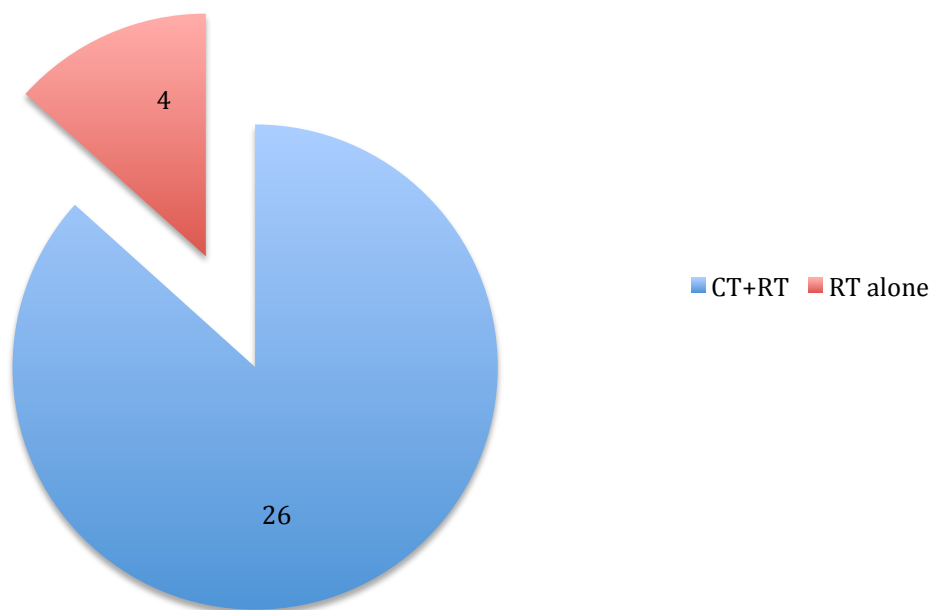
Oropharynx Stage



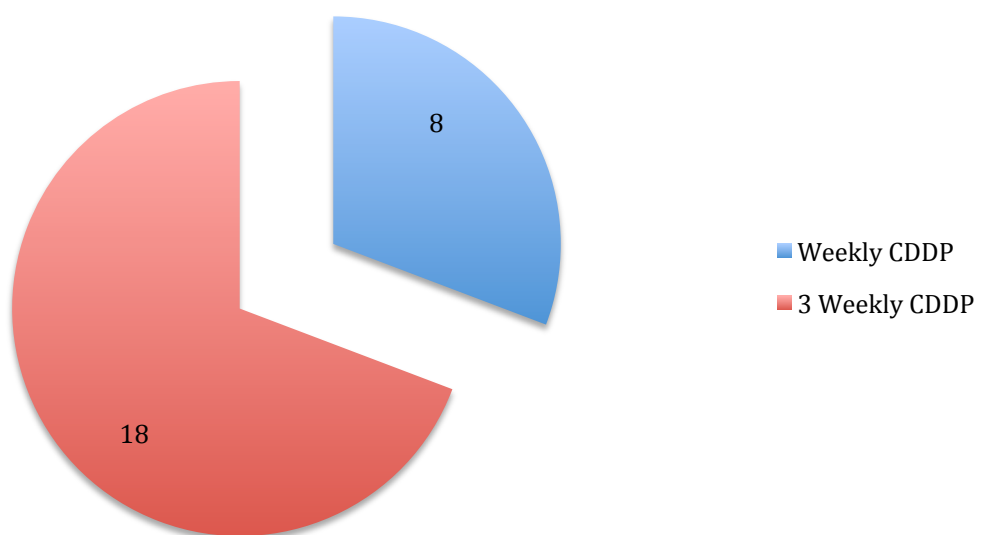
Nasopharynx Stage



Treatment



Chemotherapy



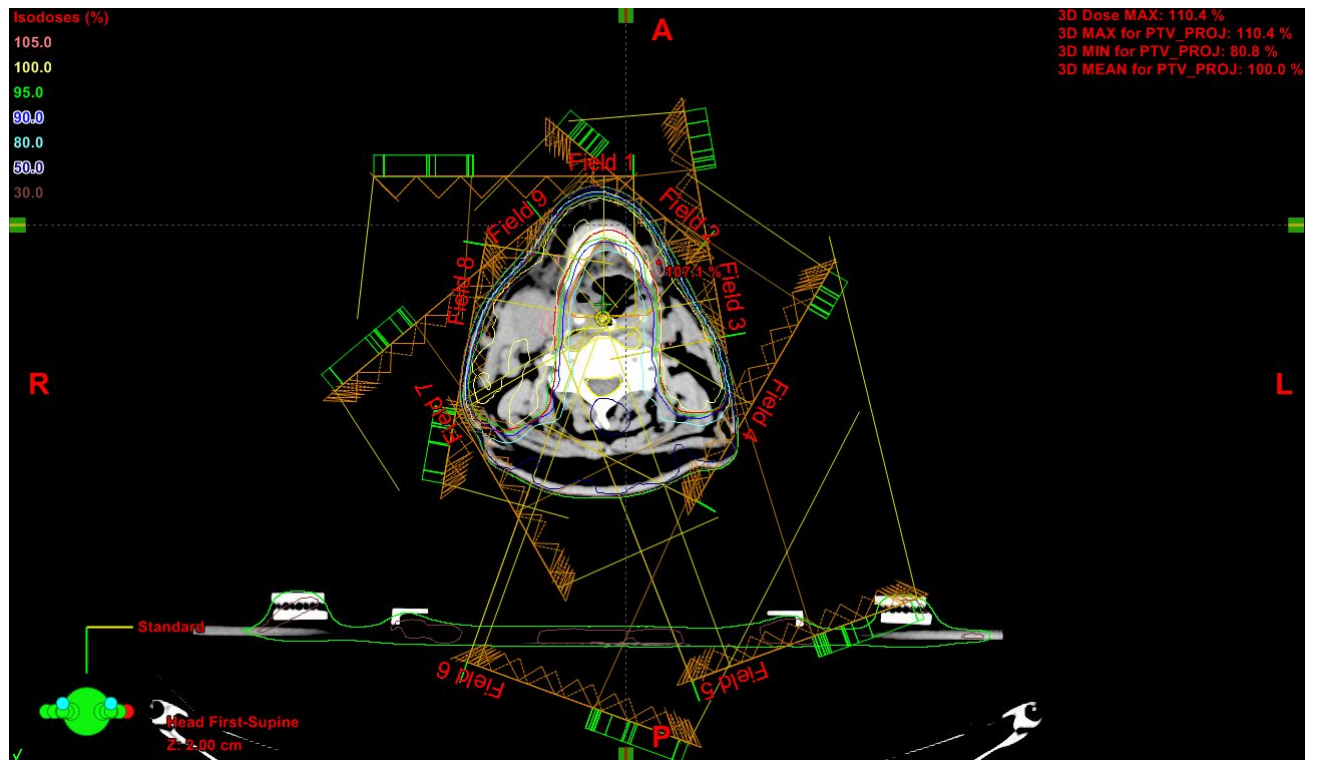
Dose Volume Characteristics

The mean doses and the volumes of these structures receiving specified doses are detailed in Table. The mean doses to the swallowing structures i.e. to the PC were kept at maximum mean dose of 56Gy, to the glottic and supraglottic larynx had maximum mean dose as 53Gy and the esophagus 59Gy. Out of the 26 patients in who optimized IMRT plans were executed and the V40, V50, V60 for all them were calculated. The mean doses to these structures co-related significantly with the volume of these structures within the PTV. The dysphagia optimized IMRT plans required up to 9 fields arrangement in order to achieve the required dose constraints. When executing the inverse plan, the requirement was to have a margin of a minimum of 5-7mm between the target volume delineation and the contour of the swallowing structures. According to our physicists at our center this was essential in order to achieve the required goal. And because of this additional margin that was required, the volume of these structures receiving 50Gy or more had considerably increased and this significantly reflected in the clinical outcome of the plan. Logically speaking, the patients with an advanced disease, bulky disease or nodes would invariably require a large target volume and in such cases defining the CTV plus a margin for the PTV greatly reduces the chance of keeping the volume of swallowing structures to a

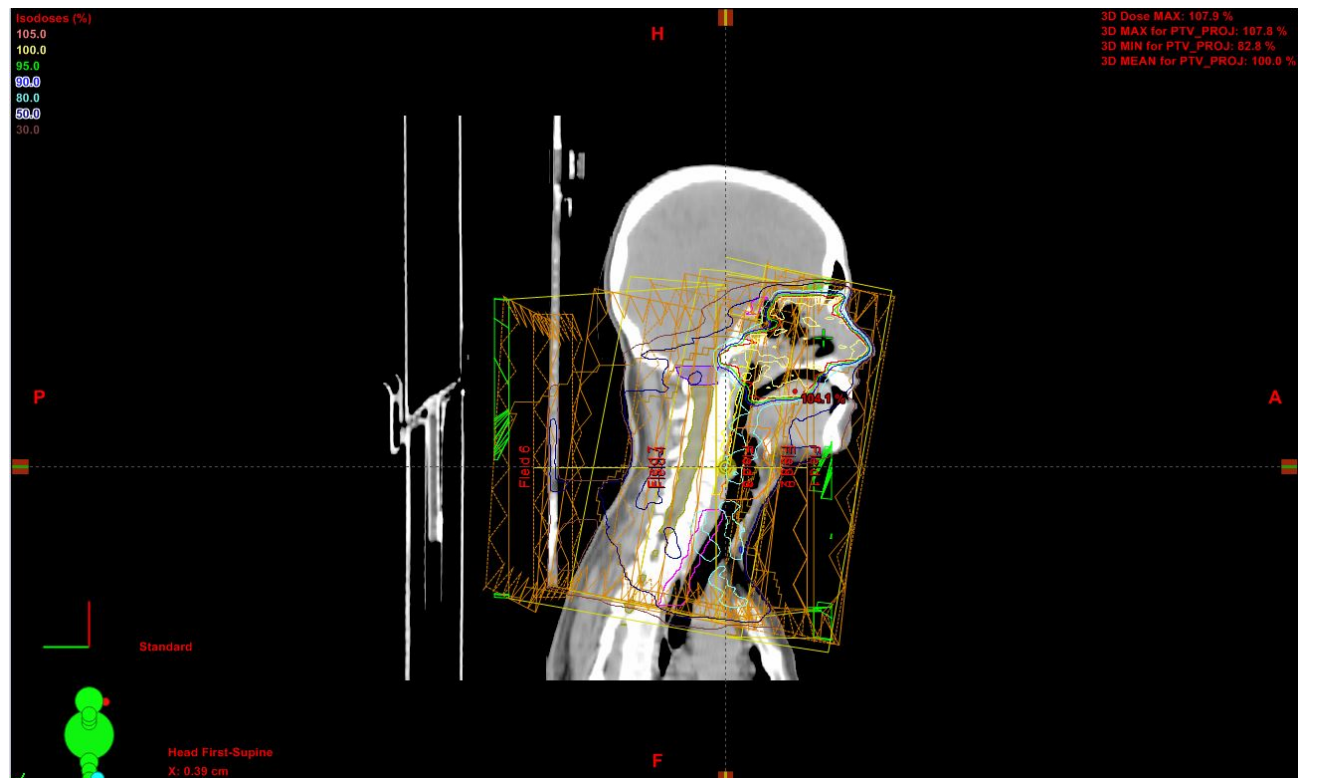
minimum. The mean dose volume percentages of the structures are given in the table.

GSL	Median
Mean Dose (Gy)	47
V40 (%)	82
V50 (%)	52
V60 (%)	44
Esophagus	
Mean Dose (Gy)	45
V40 (%)	51
V50 (%)	50
V60 (%)	16
PC	
Mean Dose (Gy)	50
V40 (%)	82
V50 (%)	49
V60 (%)	28

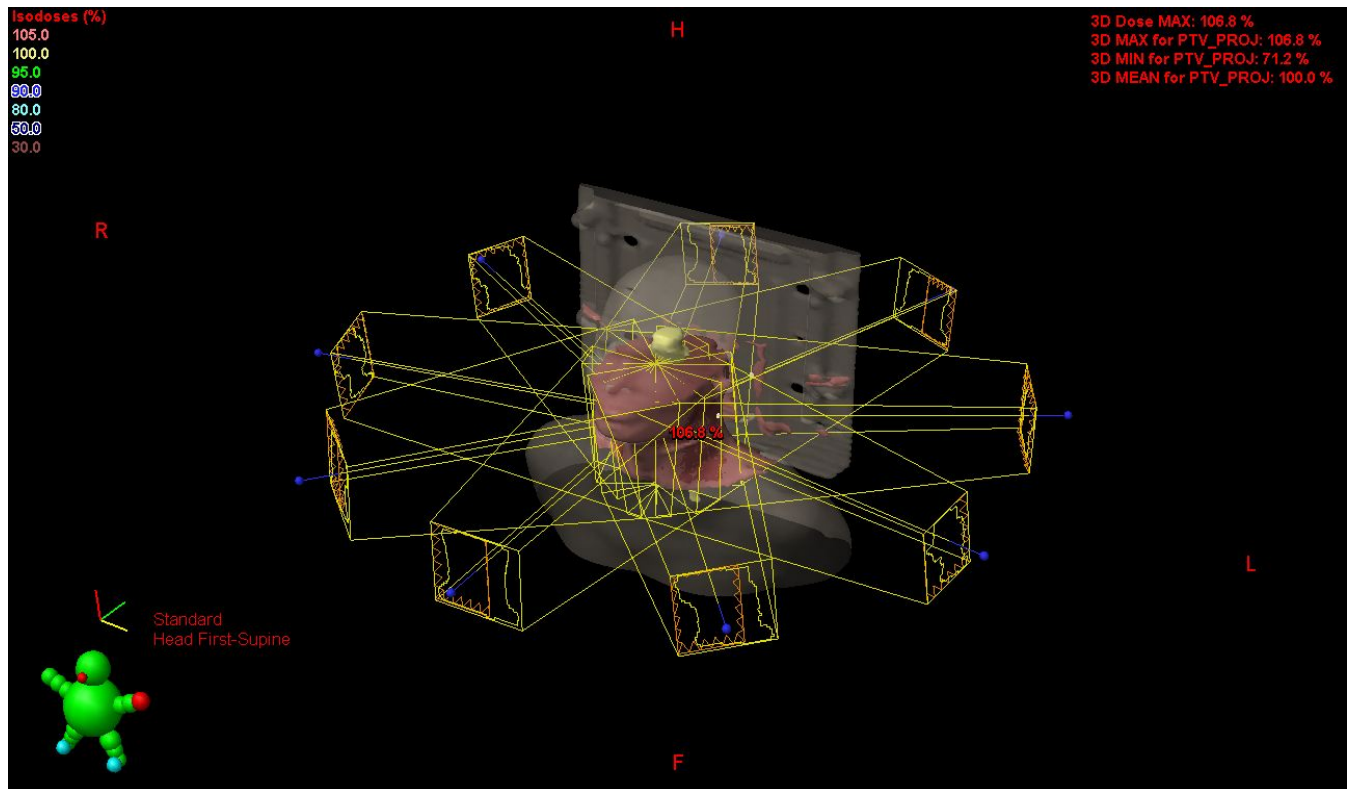
Field alignment of the optimized IMRT plan



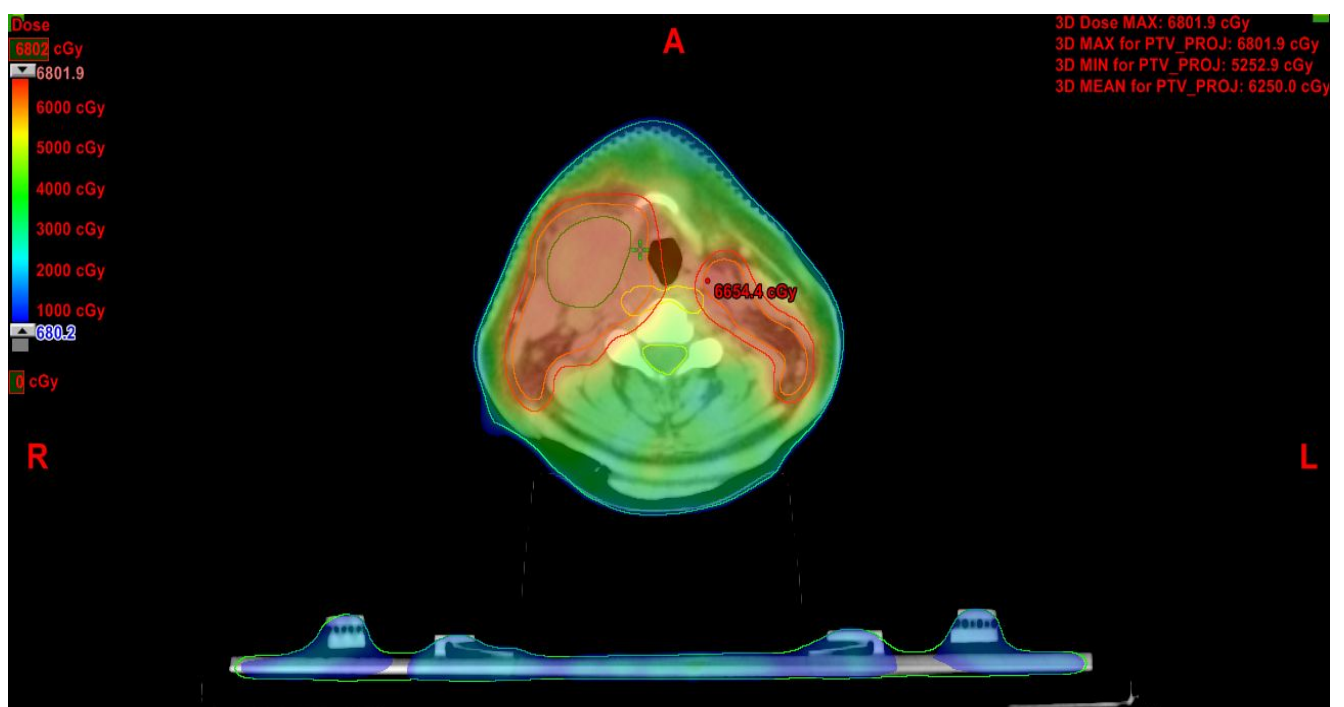
Topography of the field arrangement



Field alignment

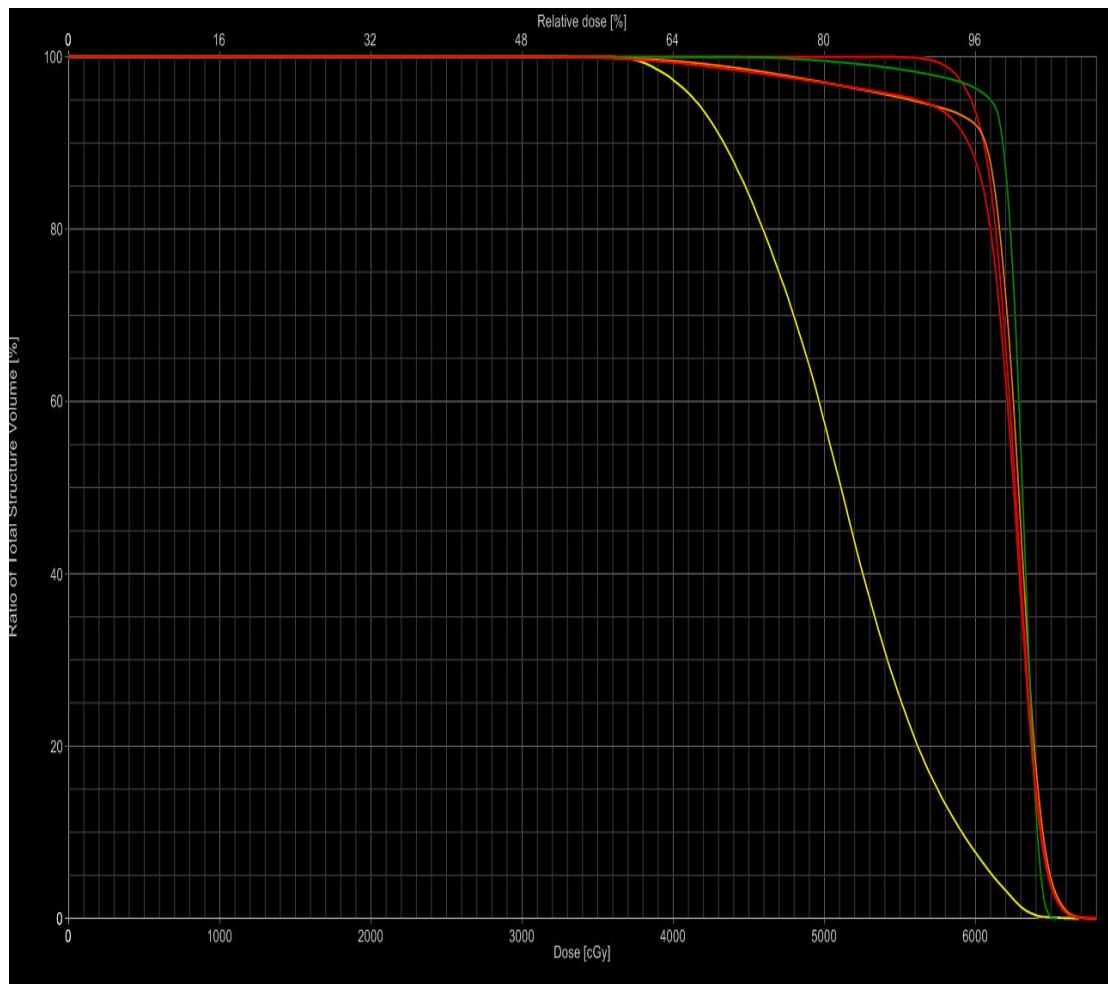


Dose colour wash in a Nasopharyngeal carcinoma patient



DVH of PC compared to the target volumes

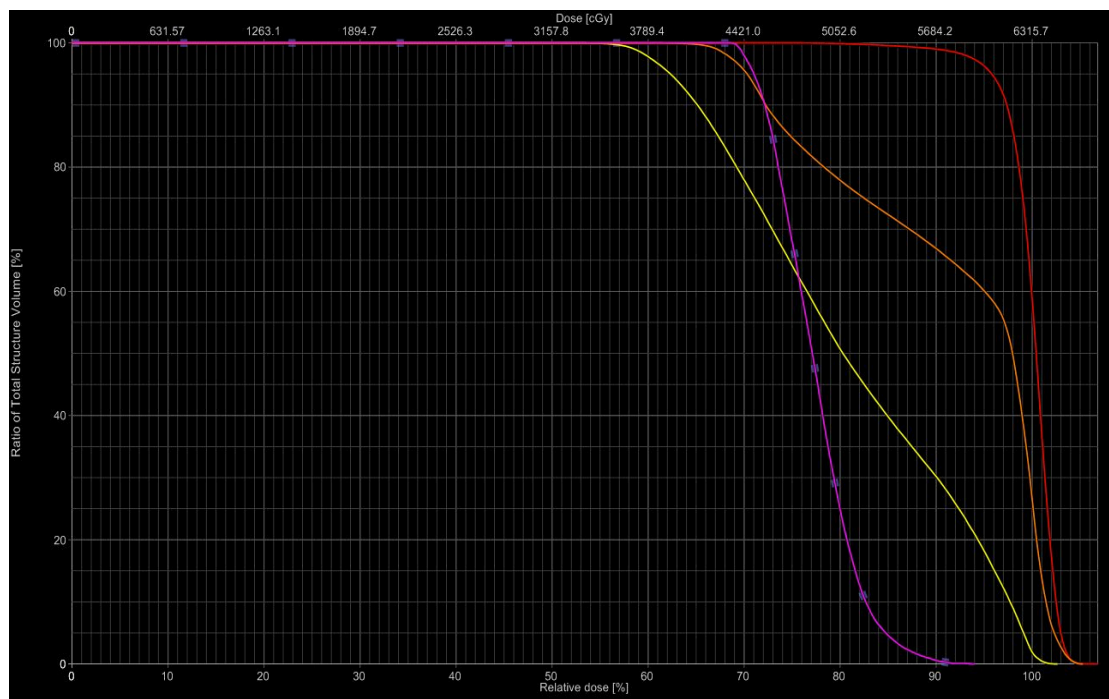
In this DVH, of a case of nasopharyngeal carcinoma, the volume of PC when compared to the target volumes is elicited. It clearly show that the volume of pharyngeal constrictors receiving the full prescribed dose i.e. 60Gy is kept at minimum where as about 60% of the volume receives 50Gy or less.



Yellow – PC, Green – GTV, Orange – CTV, Red – PTV

DVH of oropharyngeal carcinoma showing PC, GSL, ESOPHAGUS

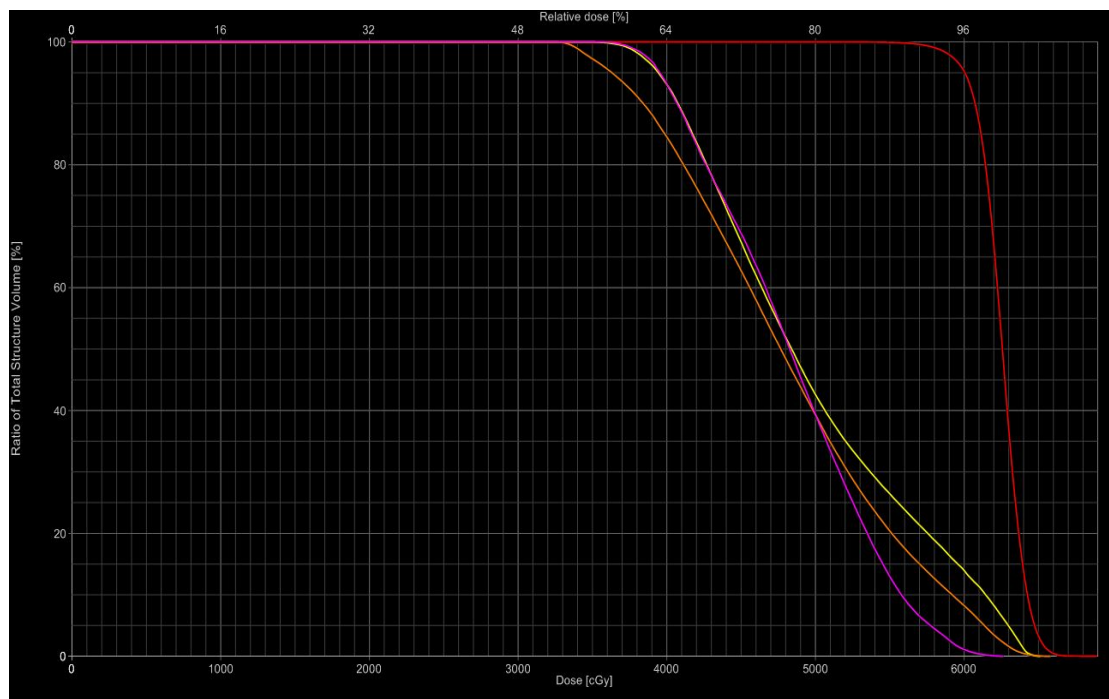
This is a case of locally advanced oropharyngeal carcinoma in which the V50 of the PC, GSL and Esophagus was 52%, 72%, and 30% respectively. Here, 100% of the volume of GSL and 99% of the volume of esophagus is receiving 40Gy. These dose volumes had significant correlation with patient reported dysphagia.



Yellow – PC, Orange - GSL, Pink – Esophagus, Red – PTV60

DVH in a case of early stage oropharyngeal carcinoma

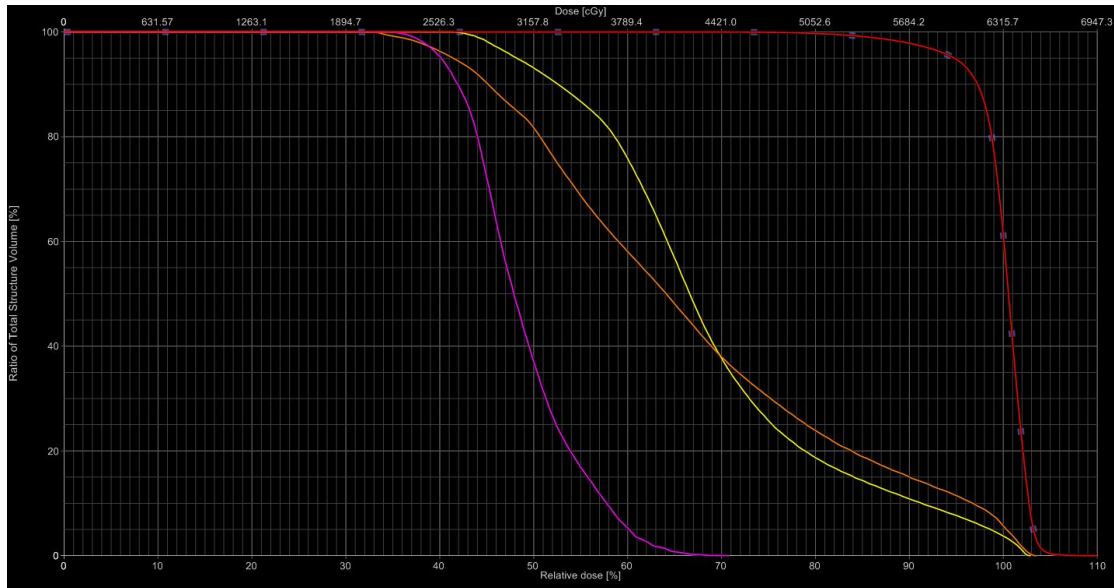
In this case as it is an early stage disease, it was noted that there is considerable increase in the volume of swallowing structures being allowed to spare. The V60 of pharyngeal constrictors was only 8% with a mean dose of 43Gy and that of GSL, Esophagus was 11% and 0% respectively. Again such sparing has shown significant co-relation with the patient reported dysphagia.



Yellow – PC, Orange - GSL, Pink – Esophagus, Red – PTV60

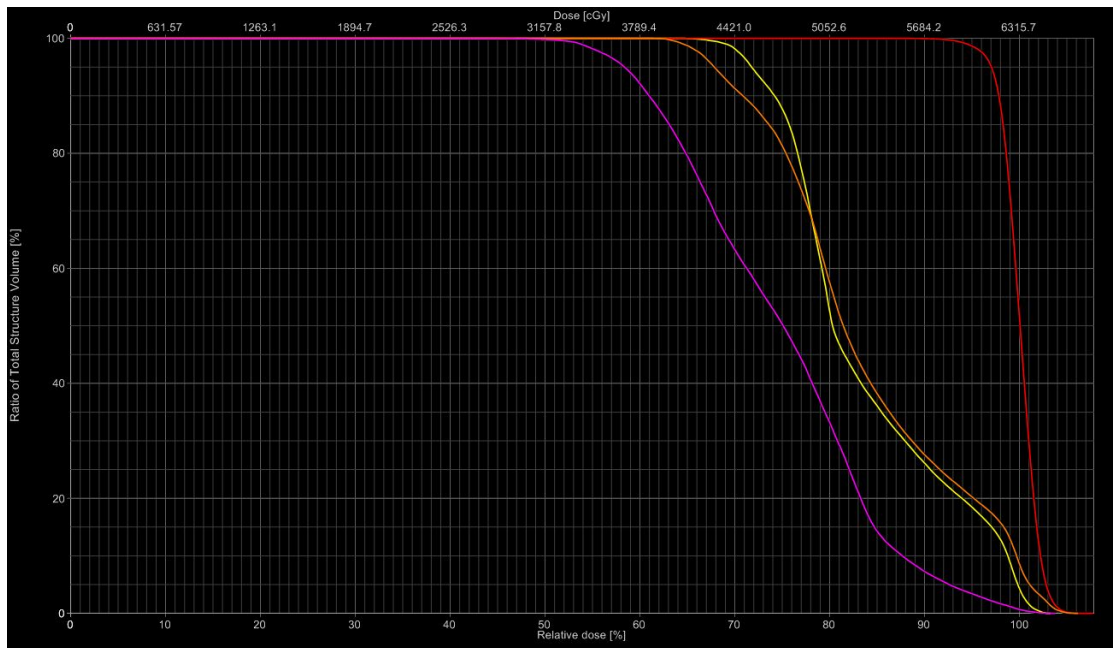
Another case of oropharyngeal carcinoma

Mean dose: PC – 43Gy; GSL - 42Gy; Esophagus – 30Gy



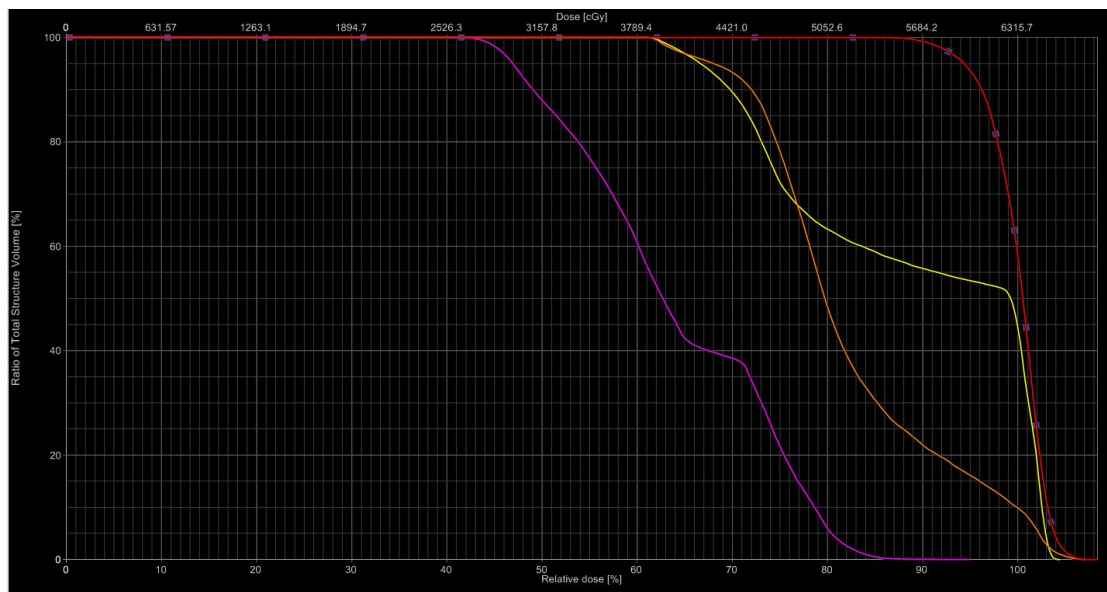
DVH in a case of Nasopharyngeal Carcinoma

In both the cases presented below, the mean dose received by the constrictors was found to be 53-54Gy and the V50 and V60 was calculated to be 60-63% and 20-40% respectively.



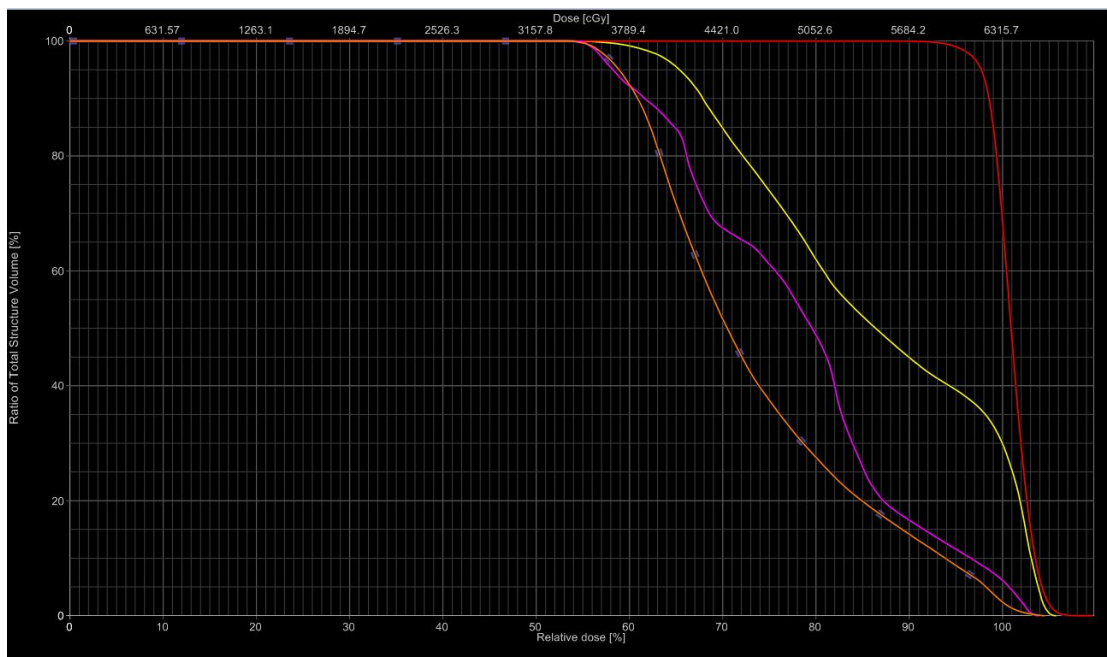
Yellow – PC, Orange - GSL, Pink – Esophagus, Red – PTV60

DVH in a case of locally advanced oropharynx with bulky node



Yellow – PC, Orange - GSL, Pink – Esophagus, Red – PTV60

DVH in a Case of Oropharynx



Yellow – PC, Orange - GSL, Pink – Esophagus, Red – PTV60

Dose-Volume Effect Relationship at 3 months post therapy:

The primary goal of this study was to reduce the volume of dysphagia related structures receiving more than 50Gy without any compromise in PTV. In each case, establishing a consensus for contouring and sparing the PC, GSL and esophagus was challenging. When the V60 of each of these cases was observed it was found that more the percentage of V60 to the constrictors, more the dysphagia. Significant co-relation was found with the constrictors and specifically the superior constrictors. In oropharyngeal carcinomas, when the disease was bulky or locally advanced, the feasibility of sparing the glottic and supra-glottic larynx without compromising the target volumes was difficult and accordingly the median of the mean dose to GSL in oropharynx was 51Gy when compared to median dose to GSL overall was only 47Gy. In a case of nasopharyngeal carcinoma, with respect the larynx the median of mean dose was 49Gy, which showed significant co-relation in terms of the epiglottic function observed in the MBS. 2% of the patients in this study were found to be gastric tube dependent at the end of 3 months, 2 of the 26 patients aspirated when compared to nil patients prior to treatment. Aspiration patients consequently showed a mean dose of 53Gy and 54Gy to the GSL, which shows a significant co-relation. Penetration was observed more in patients with oropharyngeal carcinoma i.e. 3 out of 16 patients. Among these patients, the mean dose

to the GSL was found to be around 49Gy. When co-related with patient reported dysphagia, it was found that in patients who had difficulty in swallowing liquids or the ones who were on liquid diet, the mean dose to the constrictors was 54Gy. These relationships between the volumes of dysphagia structures receiving a higher mean dose co-related significantly both clinically as well as statistically. When these results were compared to a retrospective study in which the DVH of the swallowing structures were co-related with patient reported dysphagia, there was a statistically significant difference both in DVH (PC – $p=0.005$, GSL – $p=0.008$, Esophagus – $p=0.04$) and incidence of dysphagia ($p < 0.001$).

Patient reported dysphagia – Subjective evaluation

Patient reported dysphagia was evaluated using the Head and Neck Quality of life (QOL) instrument and the University of Washington Quality of Life Questionnaire. As mentioned earlier, significant relationship was reported when the DVH of the different structures was compared to the patient related dysphagia. Out of the 26 patients, 2 patients were gastric tube dependent, more than 85% of the patients did not have any reported dysphagia at the end of 3 months post treatment. Of the remaining 4 patients, 2 patients were swallowing solids with difficulty and 2 patients were on liquid diet. Patients who were to gastric

tube dependence, one of them was a case of advanced oropharyngeal carcinoma with mean dose to swallowing structures was around 48Gy-49Gy and had residual disease. The other patient had maximum mean dose of 56Gy to the PC, 52Gy to GSL and 50Gy to esophagus. This correlation shows the clinical implication of using optimized IMRT plans and improving dysphagia.

Direct Endoscopy Findings

Direct endoscopy is another measure of swallowing dysfunction. The anatomical aspect of dysfunction can be evaluated in this way. As a routine, for all patients endoscopy was done to evaluate the disease status. It was observed that out of 26 patients, 25 patients had complete remission at first follow up. At first follow up, 90% of the patients had complaints of dysphagia and anatomically in all the patients; it was found that the arytenoids were swollen. The complaint of dysphagia could be attributed to this finding. The patient reported dysphagia in such a case could be due to pain during swallowing which is interpreted as difficulty in swallowing by some patients. Such patients are more comfortable having soft solid diet and liquid diet which in turn dictates the quality of life of such patients.

Epiglottic thickening, decreased laryngeal movement, UES dysfunction due to fibrosis and edema also translate into factors causing aspiration and dysphagia. All these findings significantly co-relate with the percentage of these structures receiving the total prescribed dose in a way that in patients with glottic dysfunction, the maximum dose to the GSL was found to be more than 55Gy and the same with epiglottis and arytenoids.

DISCUSSION

In this study of an optimized IMRT strategy aiming at reducing the dose to dysphagia related structures (PC, GSL, Esophagus) we have found statistically significant and probably clinically important dose-effect volume relationships for dysphagia and aspiration in such patients. These results thus achieved can serve as possible dosimetric goals for all patients being treated with IMRT. Avraham Eisbruch et.al (58) have hypothesized that reducing the dose to dysphagia and aspiration related structures might help improve dysphagia in patients being treated with the present day intense concurrent chemo-radiation regimens. The dose-effect volume relationships achieved in this study support the hypothesis that by reducing the dose and the volume of the dysphagia related structures receiving target dose (i.e., volume of these structures coming within the PTV) can clinically improve treatment related dysphagia. The subsequent issue with such a hypothesis is that, such a study can support the hypothesis but will not be able to prove it because we could not establish a cause - effect relationship. However it definitely establishes a need to try and further reduce the dose to these structures without compromising the PTV. The limiting factor in this is the percentage of volume of these structures, which come within the PTV, and this correlates strongly with the mean dose achieved for these structures.

The first step in achieving improved sparing of these structures by is avoiding setup errors by daily on board imaging and correction of these errors (78). The setup errors should be kept at as minimum as possible (i.e. $1 \pm 0.5\text{mm}$). Another valid way to accomplish this is to eliminate the PTVs and construction of IMRT plans that cover the CTVs and their known distribution of setup uncertainties. Other options including adaptive radiotherapy (or) proton beam IMRT (or) structure and target assessments.

It was found that the dose volume effect relationships regarding aspiration could be related clinically the strongest in pharyngeal constrictors as a single organ including each of its parts, superior pharyngeal constrictor, middle pharyngeal constrictor and inferior constrictors. This relationship was statistically strongest for the superior pharyngeal constrictor. The importance of the superior constrictor regarding the dose volume effect relationship can be explained by the mechanism of swallowing. Elevation of larynx and pharynx and the closure of epiglottis are essential for airway protection as well as bolus propulsion. This mechanism is possible with the contraction of longitudinal muscles (glossopharyngeus, stylopharyngeus, palatopharyngeus and salpingopharyngeus) which blend with the circular muscles of the superior constrictor (79). As these muscles pull the pharynx and the

larynx upward and forward, away from the lower posterior pharyngeal wall which will allow the upper esophageal sphincter to open at the cricopharyngeus muscle (80). This mechanism of swallowing when correlated to the acquired objective results based on MBS of this study suggest that it is more beneficial to try and reduce the volume of superior constrictor receiving more than 50Gy than confining the constraint to the upper esophagus near the area of the inlet. The subjective results of this study also suggest the importance of sparing the superior constrictor when compared to middle and inferior constrictors. A recently conducted study in which brachytherapy was found to reduce dysphagia concluded that the doses to the superior and middle constrictors was the most significant predictors of patient-reported dysphagia (81). Significant dose volume effect correlations were found in GSL and dysphagia as well. A lot of recently conducted studies showed significant relationship between dysphagia and dose received by the glottic (82) and supraglottic larynx (82,83). Similar co-relations were found in our longitudinal study as well, in which the end-point comparison between pre and post-therapy dysphagia rather than dysphagia after radiation alone. This affirms that there is potential benefit in reducing the volume of glottic and supraglottic larynx receiving radiation therapy.

The dose volume effect relationships for the swallowing structures depend on the chemo-radiation regimen as well. In the present study, no strictures were found when mean dose received by the PC was <66Gy. In addition in another study it was found that after an intensive gemcitabine radiation regimen, the minimal dose associated with strictures was 50Gy(56). Such differences in effect of intensity of dysphagia and aspiration based on chemo radiation regimens may be due to the intensity of acute mucositis and its effect on the pharyngeal tissue. Chemo-RT regimens, which do not differ in the intensity of acute mucositis seem to cause similar rate and types of swallowing abnormalities (59).

In this study, the relative homogeneity of patient population, most of whom were oropharynx patients may have helped in identifying the dose effect relationship of the swallowing structures. Also, in this study we have observed dose volume relationships 3 months post therapy, and these relationships may change if observed over longer time duration (i.e. 6,12,24 months) post therapy. Swallowing seems to reach a steady state at around 12 months when edema subsides and long-term fibrosis sets in (84). The only way this issue could be addressed is that if we collect data for up to 24 months post therapy. Swallowing related pharyngeal and laryngeal motion may affect the dose delivered to these structures when compared to the simulation CTs. Studies based on of

these effects found that the incidence and duration of swallowing during RT is very low, averaging 0.45% (range, 0–1.5%) of the total irradiation time (85). In our study, the mean doses received by the swallowing structures were found to significantly correlate with the percentages of these structures within the PTVs. In a previous study, it was found that the percentages of these structures within the PTV did not change significantly with their expansion in order to produce planning organ-at-risk volumes was made, when compared with the non-expanded structures (58). Such data suggests that when the swallowing structures are expanded in order to obtain their respective organ-at-risk volumes will not substantially change the planning, optimization and results of our study. This issue has to be investigated further. As detailed earlier in the material and methods, we have taken only the lateral RP nodes into consideration not the medial ones for the nodal CTVs only when RP nodes were considered to be of high risk (unless the lateral RP nodes were grossly involved). This method facilitated the possibility of partial sparing of the PC and the upper part of GSL. Several RP nodal failures have been reported in patients being treated with IMRT and most of them were found to be in the lateral RP space, medial to the carotid artery (61). McLaughlin et al. (63) stated that the medial RP nodes have not often been recognized as sites of cancer metastases. The literature search found several series of head-and-neck cancer that detailed involvement of the

lateral and medial RP nodes (63–73). These series showed a very low risk of medial RP nodal involvement; in 10 series a cumulative report of about 600 patients with RP nodal involvement or enlargement showed that 98% of the patients showed lateral RP nodal involvement and 2% showed medial RP nodes. One of these series detailed the results of dissection of 11 cadavers and 9 of them showed lateral RP nodes (73). In our study, the afferent lymphatics from Nasopharynx and Oropharynx were found to be flowing into the lateral RP nodes whereas the medial nodes received lymphatics from the posterior pharyngeal wall. These series suggest that in almost all cases in which the RP nodes are at risk show that lateral RP nodes are at substantial risk of involvement (except for the posterior pharyngeal wall tumours). However the actual consequence of under dosing the medial RP nodes is not yet clearly known as the lymphatic channels transverse through the medial RP space. The under dosing becomes an issue because sparing of the swallowing structures results in steeper dose fall-off near the targets in the vicinity of these structures (58), compared with IMRT plans that do not include such modified IMRT plans. Therefore, outlining the targets requires a high level of precaution so that the target volumes do not get compromised or under dosed taking into account the uncertainty of defining the mucosal gross tumour volume using the available imaging modalities (86). This forms the basis for our optimized IMRT plan for this study, i.e., not to

compromise the target volume under any circumstances. Thus, so far in this study within a median follow up of about 12 months, only two failures have occurred and the failure was within the previously prescribed GTV, which were given the full-prescribed dose.

Table 8. Lateral vs. medial retropharyngeal (RP) nodes in series that detailed the sites of involved/detected RP nodes

Authors (reference)	Patients evaluated	No. of patients evaluated	Evaluation method	No. of patients with RP nodes	No. (%) of patients with lateral RP nodes	No. (%) of patients with medial RP nodes
Mancuso <i>et al.</i> (11)	Head and neck cancer	30	CT	20	20 (100)	0
Bussels <i>et al.</i> (13)	Oropharyngeal cancer	209	CT	33	32 (97)	1 (3)
Poon <i>et al.</i> (12)	Head and neck cancer	35	CT	89*	84* (94)	5* (6)
Chong <i>et al.</i> (14)	Nasopharyngeal cancer	114	CT	59	59 (100)	0
King <i>et al.</i> (15)	Nasopharyngeal cancer	150	CT	108	108 (100)	0
Liu <i>et al.</i> (16)	Nasopharyngeal cancer	275	MRI	175	174 (99.6)	1 (0.4)
Ng <i>et al.</i> (17)	Nasopharyngeal cancer	89	MRI, PET	73	73 (100)	1 (1.5) [†]
Lam <i>et al.</i> (18)	Nasopharyngeal cancer	44	MRI	39	37 (95)	2 (5)
Ozlugedic <i>et al.</i> (19)	Noncancer	12	Dissection	6	6 (100)	0
Saito <i>et al.</i> (20)	Noncancer	11	Dissection	10	9 (90)	1 (10)

Abbreviations: RP=retropharyngeal; CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography.

* This series provided only the number of identified nodes at each nodal site, not patient numbers.

[†] One patient in this series had both lateral and medial involved RP nodes.

The prescribed IMRT plan in our study included the whole neck. Another approach to this is to include the plan for the primary and upper neck and to match the same with a low anterior neck field at the thyroid notch with a midline laryngeal block. This results in lower doses to the GSL (87,88) but the issue with such an approach is that in cases, which have a high risk of posterior deep neck nodal involvement, cases might

result in under-dosing of these deep lying targets. This might be a reason for some reported lower neck failures (89,90).

CONCLUSION

We can conclude that sparing the swallowing structures using optimized IMRT, is feasible. It was found that the relationship between the dose volume values for the swallowing structures and the objective and subjective measures of dysphagia was statistically significant and clinically relevant. In an attempt to obtain such goals, it is very important not to forget the importance of avoiding missing or under dosing the target volumes. These thus found relationships could now be used to prescribe optimized goals and thus push forward more efforts in order to reduce the dose to these structures further. This also improves the QOL of these patients and serves the purpose of organ and function preservation when chemo-radiation is used as the treatment modality rather than surgery. There is a need to observe long-term results in order to obtain stronger results in terms of disease recurrence or survival.

In terms of statistical significance of this study, it is recommended to try and reduce the dose to the swallowing structures. The question is whether it is a possibility in terms of availability of expertise, time consumption and logistics in a country like India. Cost vs benefit analyses of such a study is something that can be considered. Implementation of such a strategy using IMRT technique helps to improve QOL of head and neck cancer patients but the feasibility of such a study in an Indian scenario is questionable.